REVIEW Biomedical Engineering

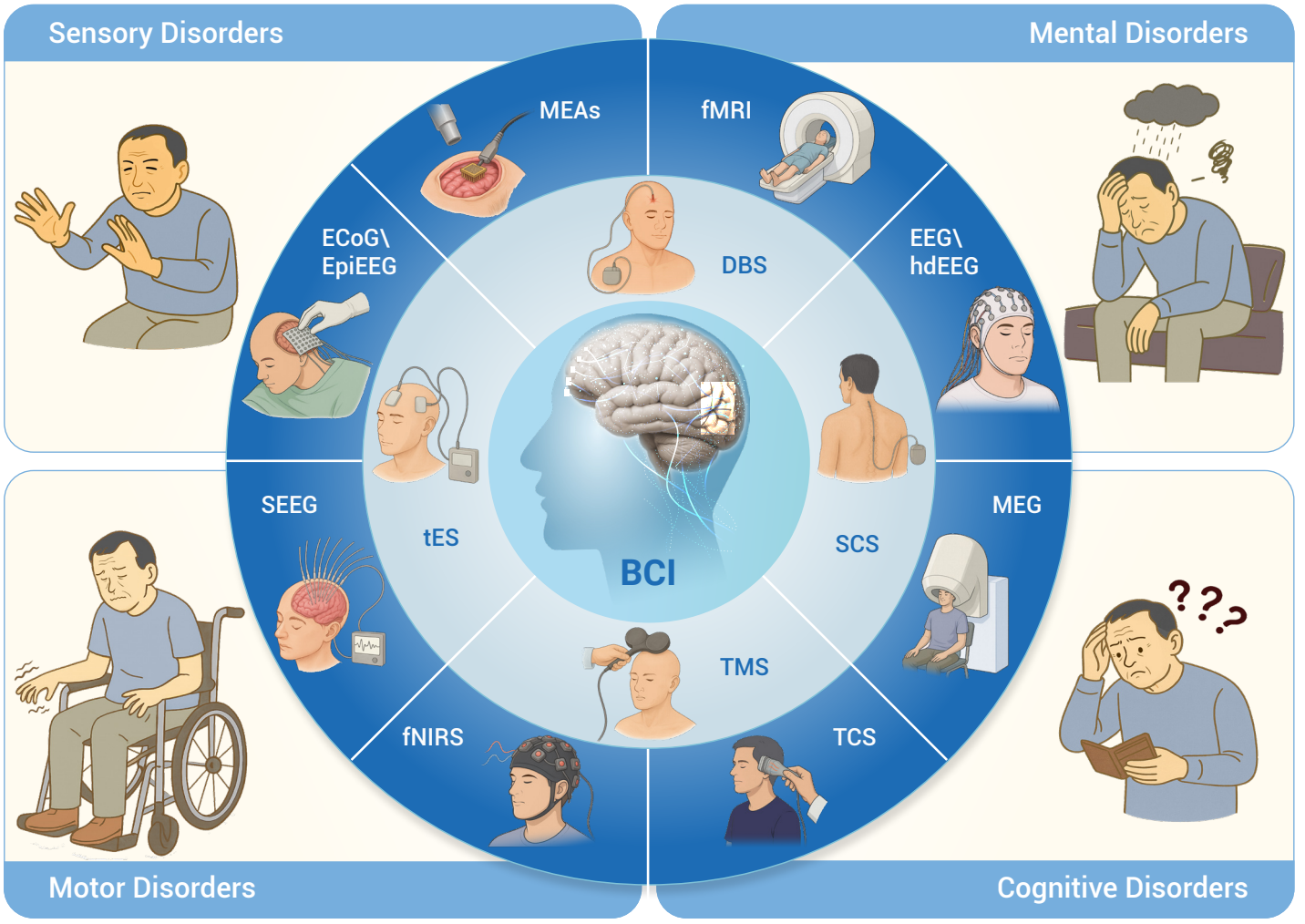
A brain-computer interface roadmap for diagnosing and treating neurological disorders

Gengchen Sun,[1,6] Yimeng Wang,[2,6] Hongxing Liu,[2,6] Longer Weng,[2,6] Xinjie Li,[3,6] Wenjun He,[1] Jiaqi Sun,[1] Sicheng Liang,[1] Wenqi Kong,[1] Jing-Zheng Dong,[3,4] Jiawang Li,[2] Shu Zheng,[2] Yan-Xue Xue,[3,5,*] Lin Meng,[2,*] Guangjian Ni,[2,*] Chenguang Zheng,[2,*] Biao Sun,[1,*] and Dong Ming[2,*]

*Correspondence: yanxuexue@bjmu.edu.cn (Y.X.); linmeng@tju.edu.cn (L.M.); niguangjian@tju.edu.cn (G.N.); cgzhengnk@gmail.com (C.Z.); sunbiao@tju.edu.cn (B.S.); richardming@tju.edu.cn (D.M.)

Received: October 5, 2025; Accepted: November 7, 2025; Published Online: November 8, 2025; https://doi.org/10.59717/j.xinn-inform.2025.100016

GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Brain-computer interfaces (BCI) achieve the treatment of neurological diseases through decoding and modulation.
- BCI can provide personalized treatment for neurological diseases through closed-loop neuromodulation.
- Key challenges include decoding accuracy, long-term biocompatibility, and real-world clinical translation.

OPEN ACCESS

Biomedical Engineering REVIEW

The Innovation Informatics

A brain-computer interface roadmap for diagnosing and treating neurological disorders

Gengchen Sun,[1,6] Yimeng Wang,[2,6] Hongxing Liu,[2,6] Longer Weng,[2,6] Xinjie Li,[3,6] Wenjun He,[1] Jiaqi Sun,[1] Sicheng Liang,[1] Wenqi Kong,[1] Jing-Zheng Dong,[3,4] Jiawang Li,[2] Shu Zheng,[2] Yan-Xue Xue,[3,5,*] Lin Meng,[2,*] Guangjian Ni,[2,*] Chenguang Zheng,[2,*] Biao Sun,[1,*] and Dong Ming[2,*]

[1]School of Electrical and Information Engineering, Tianjin University, Tianjin 300072, China

[2]Medical School, Tianjin University, Tianjin 300072, China

[3]National Institute on Drug Dependence, Beijing Key Laboratory of Drug Dependence, Peking University, Beijing 100191, China

[4]School of Automation and Electrical Engineering, Inner Mongolia University of Science and Technology, Inner Mongolia 014010, China

[5]Chinese Institute for Brain Research, Beijing 102206, China

[6]These authors contributed equally

*Correspondence: yanxuexue@bjmu.edu.cn (Y.X.); linmeng@tju.edu.cn (L.M.); niguangjian@tju.edu.cn (G.N.); cgzhengnk@gmail.com (C.Z.); sunbiao@tju.edu.cn (B.S.); richardming@tju.edu.cn (D.M.)

Received: October 5, 2025; Accepted: November 7, 2025; Published Online: November 8, 2025; https://doi.org/10.59717/j.xinn-inform.2025.100016

Citation: Sun G., Wang Y., Liu H., et al. (2025). A brain-computer interface roadmap for diagnosing and treating neurological disorders. *The Innovation Informatics* **1**:100016.

Currently, the global incidence of neurological disorders is on a continuous upward trend, posing severe challenges to the medical field. However, traditional diagnosis and treatment methods for such diseases are associated with risks arising from invasive procedures, generally low diagnostic and therapeutic efficiency, and more critically, they struggle to achieve precise and personalized treatment, failing to fully meet the individual needs of patients. Against this backdrop, exploring rapid, efficient, and safe diagnosis and treatment protocols for brain diseases has become a core research direction. The emergence of Brain-computer interface (BCI) technology provides a highly promising solution to break through this dilemma and is expected to fundamentally revolutionize the diagnostic and therapeutic models for neurological diseases. By accurately capturing and analyzing brain signals, BCI offers a brand-new pathway for restoring lost physiological functions in patients, as well as regulating and enhancing brain activity, bringing new hope to numerous patients afflicted by neurological disorders. Here we systematically review the latest research progress of BCI technology in recent years and focus on analyzing its potential clinical application value in the fields of sensory disorders, motor disorders, cognitive disorders, and mental disorders. The research insights and technical directions summarized in this review aim to provide inspiration for subsequent research in this field, promote the development of BCI technology towards a more mature and practical direction, and ultimately provide more effective diagnostic and therapeutic means for patients with neurological disorders, helping them improve their quality of life and regain hope for health.

INTRODUCTION

The human brain, as the most complex organ of the body, governs perception, movement, cognition, and emotion through intricate neural networks and electrochemical signaling.[1] When these mechanisms are disrupted by neurological disorders, patients may suffer from severe impairments that significantly reduce quality of life. Traditional treatments, such as pharmacological interventions and neurosurgical procedures, often provide limited efficacy or induce side effects, highlighting the urgent need for more precise and personalized therapeutic strategies.[2]

Brain–computer interface (BCI) technology has emerged as a promising interdisciplinary field bridging neuroscience, engineering, computer science, and clinical medicine.[3-5] By directly decoding neural activity and establishing real-time communication pathways between the brain and external devices, BCI not only enables motor and sensory restoration but also offers novel diagnostic and therapeutic opportunities for neurological disorders.[6-8] In recent years, advances in signal acquisition, machine learning algorithms, and closed-loop neuromodulation have accelerated the translation of BCI from laboratory demonstrations to clinical applications.[9]

Importantly, BCI applications are expanding beyond motor rehabilitation to encompass a wide spectrum of neurological and mental disorders.[10] For instance, sensory BCI has shown potential in vision and hearing restoration for patients with sensory deficits, motor BCI supports functional recovery in stroke and spinal cord injury, cognitive BCI can enhance memory and attention in individuals with cognitive decline, and psychiatric BCI open new possibilities for monitoring and treating depression, anxiety, and schizophrenia. These developments suggest that BCI technology may evolve into powerful tools for disease diagnosis, prognosis prediction, and individualized therapy.[11-13]

Despite remarkable progress, significant challenges remain, including limitations in decoding accuracy, long-term biocompatibility of neural implants, ethical concerns, and the integration of multimodal neural signals into clinically viable systems. Addressing these barriers will require close collaboration across disciplines, as well as rigorous clinical validation.[14]

In this review, we systematically summarize recent advances in BCI technology and its applications in the diagnosis and therapy of neurological disorders. We first introduce the fundamental principles and technological foundations of BCI systems, then delve into its applications across four key domains: sensory, motor, cognitive, and mental disorders. Finally, we discuss current challenges and future directions for the clinical translation of BCI.

PRINCIPLES AND TECHNOLOGIES OF BRAIN-COMPUTER INTERFACES

Bidirectional information interaction in BCI

BCI is a pivotal technology that establishes a direct communication pathway between the brain and external devices. Its core goal lies in bidirectional information interaction. On one hand, it interprets the intent or state information contained in brain activity, converts it into executable commands to control external devices. On the other hand, it can encode external information into specific neural stimulation patterns and deliver them into the brain, thereby restoring or enhancing neural functions through precise neuromodulation. Based on differences in their ultimate technological goals, BCI technology can be broadly divided into two main categories: neural sensing technology and neuromodulation technology, as shown in Figure 1.

Among them, neural sensing technology is based on multimodal methods such as electricity, magnetism, light, and ultrasound. It realizes the decoding of brain intent by collecting and in-depth analyzing brain signals.[15-17] The results of this decoding have multiple application values. It can not only accurately reveal the real-time states of the brain, such as fatigue, emotion, and cognition, but also be converted into control commands to drive external devices like drones and wheelchairs to complete designated actions. At the same time, the brain intent information obtained from the decoding can also be used as a reference for brain stimulation parameters, providing support for more precise subsequent neural modulation. With the core goal of restoring, replacing, and enhancing neural functions, the technology that utilizes parameters derived from neural sensing signals to achieve precise neural modulation is defined as neuromodulation technology.

It is particularly important to note that the brain has clear functional zoning characteristics: the frontal lobe dominates advanced cognitive functions such as decision-making and planning, the temporal lobe is deeply involved in auditory signal processing and memory formation, and the occipital lobe is the core area for visual information integration. The specificity of these function determines that the diagnosis and treatment of different neurological disorders need to precisely anchor the corresponding functional brain

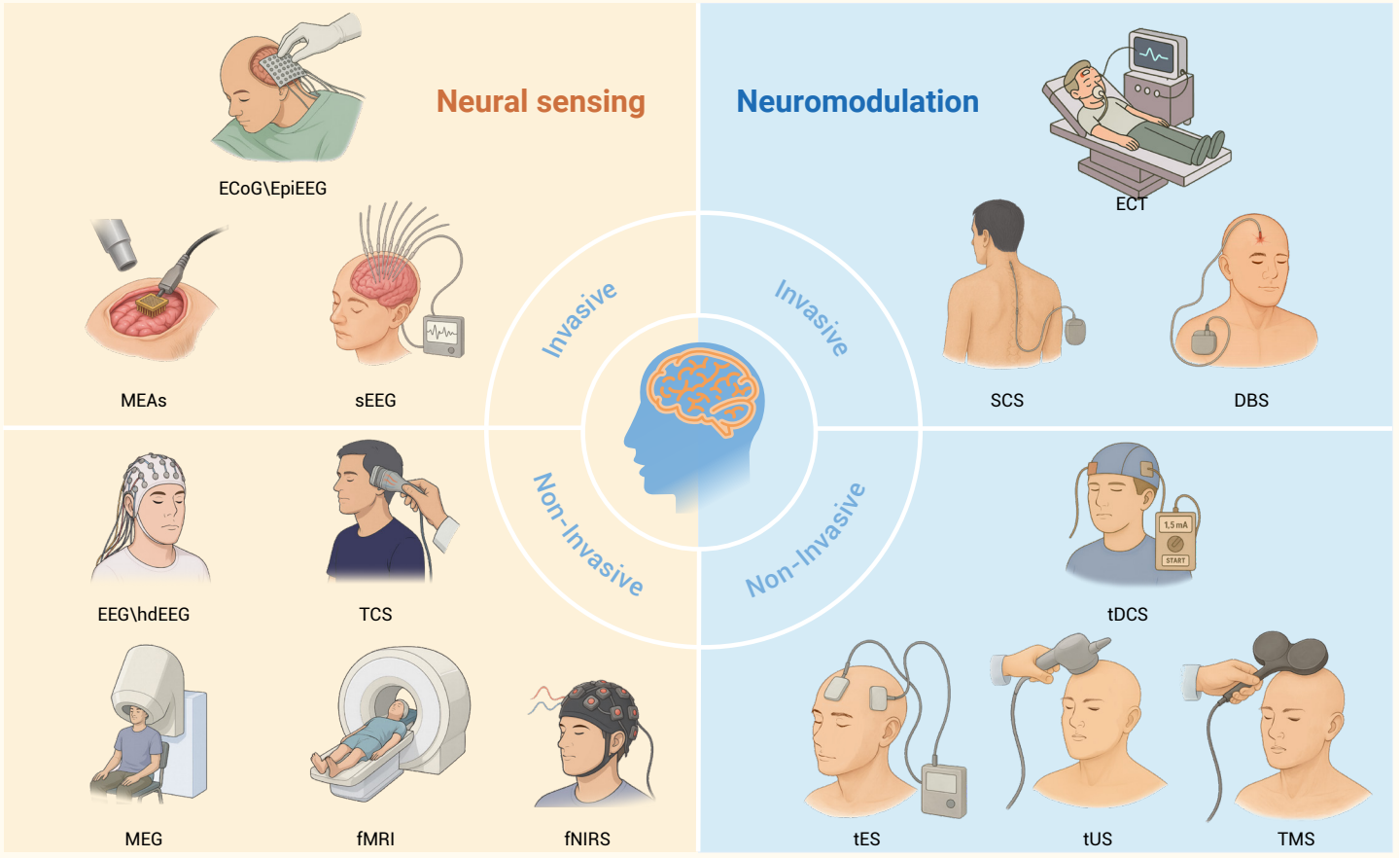


Figure 1. Neural sensing and neuromodulation technology.

regions. For instance, when treating Parkinson's disease (PD), it is necessary to focus on targeted regulation of the basal ganglia region. When improving the symptoms of depression, it is necessary to focus on the prefrontal lobe region. The specific functions of each brain region can be found in Figure 2. It is precisely because of the significant differences in brain regions of disorders target that a single technical approach is difficult to meet the diverse diagnostic and therapeutic needs. Therefore, different technical solutions must be selected specifically. Based on this core logic, we have systematically sorted out and summarized a variety of adaptive technical means around different diagnosis and treatment scenarios of neurological disorders.

Neural sensing technology

Neural sensing technology is premised on the decoding of neural mechanisms. employs multimodal signal acquisition and imaging technologies—including electrical, magnetic, optical, and ultrasonic methods—to capture brain activity. The information obtained enables precise monitoring of brain states, serving a range of core objectives from assessing cognitive function and diagnosing neurological diseases to advancing human-computer interaction. Based on the method of signal acquisition, it is broadly categorized into invasive and non-invasive types.[18-20]

Electroencephalography (EEG) serves as the fundamental form of non-invasive electrical signal sensing technology. It involves placing electrodes at specific locations on the scalp to capture the weak electrical signals generated by the synchronous firing of groups of brain neurons, and then converting these signals into visual waveform graphs.[21,22] This technology enables real-time recording of the dynamic changes in brain electrical activity. However, EEG signals are susceptible to interference from scalp oil, muscle activity, and environmental electromagnetic sources. Additionally, they have low spatial resolution, making it difficult to accurately locate the brain regions from which the signals originate.[23] High-Density Electroencephalography (hdEEG) represents a technological advancement based on traditional EEG. Its core improvement lies in a significant increase in the number of electrodes and the optimization of electrode arrangement density, allowing electrodes to cover the entire scalp more evenly. A greater number of electrodes can capture more subtle differences in EEG signals. When combined with signal source localization algorithms, this technology can enhance the spatial resolution of EEG signals to the millimeter level, enabling more accurate localization of the positions of neuron clusters that generate electrical signals.[24]

Magnetoencephalography (MEG) is the core form of non-invasive magnetic signal sensing technology. It uses highly sensitive magnetic sensors to capture the weak magnetic field signals generated concurrently with the synchronous firing of groups of brain neurons, and converts these signals into dynamic distribution maps of magnetoencephalographic activity. This technology enables real-time tracking of the spatiotemporal changes in brain functional activities. Moreover, the propagation of magnetic field signals is not interfered by biological tissues such as the scalp and skull, allowing it to more truly reflect the original activity state of neurons.[25]

Functional Magnetic Resonance Imaging (fMRI) is a non-invasive brain function monitoring method based on magnetic resonance technology. In a strong magnetic field environment, it detects the differences in magnetic resonance signals caused by changes in local blood flow and metabolism when brain neurons are activated, and then generates three-dimensional images of brain functional activities. This technology features high spatial resolution, enabling clear localization of the anatomical positions of activated brain regions. Additionally, it can simultaneously achieve combined imaging of brain structure and function, providing abundant information for neurological disorder diagnosis and neuroscience research.[26-29]

Functional Near-Infrared Spectroscopy (fNIRS), a mainstream non-invasive optical sensing technology, measures brain activity by emitting near-infrared light (700-900 nm) into the brain tissue through source-detector modules placed on the scalp and then detecting the scattered and absorbed signals.[30] Combined with optical algorithms, it infers the concentration changes of oxyhemoglobin and deoxyhemoglobin in the brain, thereby indirectly reflecting the activity state of neurons. This technology can monitor the dynamic changes of brain functional metabolism in real time, and does not

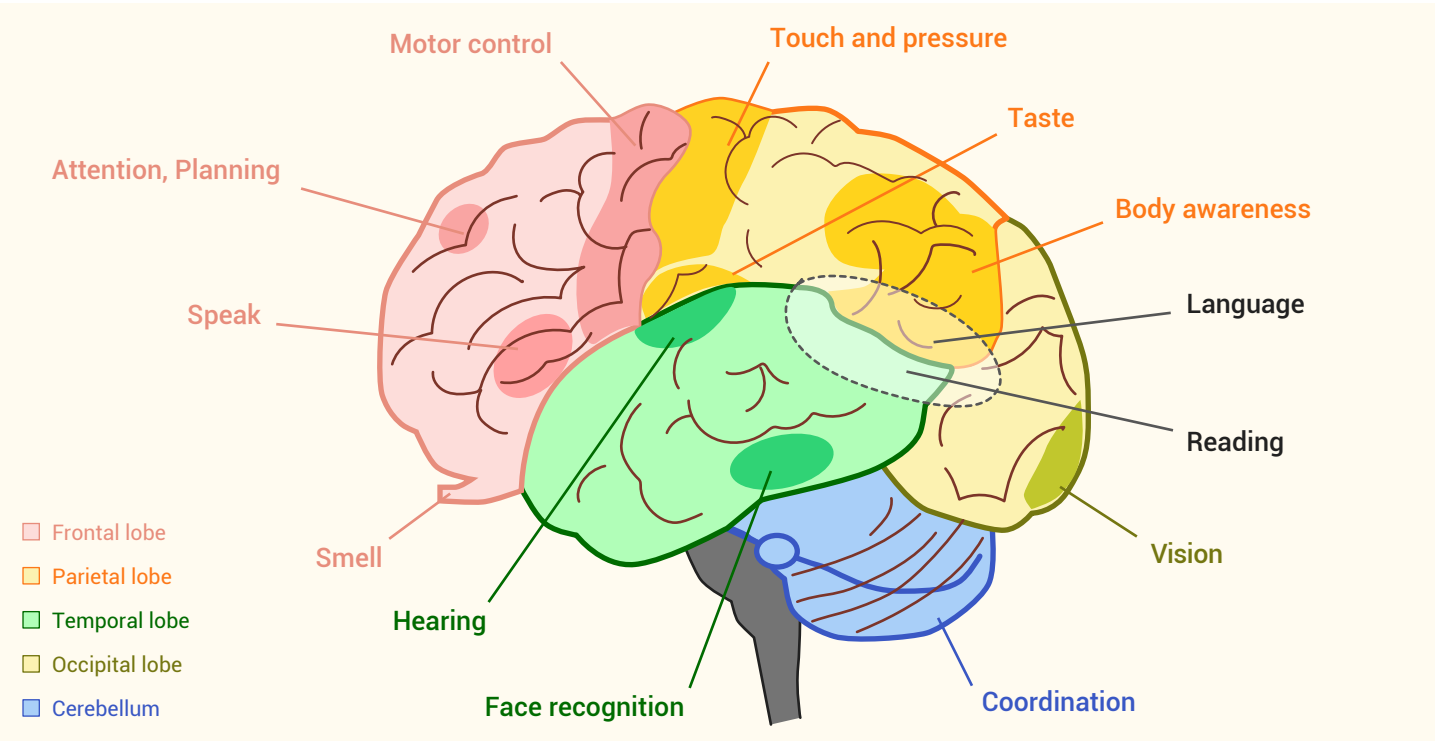


Figure 2. Reference diagram for the specific functions of each region of the brain.

require a complex fixed environment, allowing monitoring to be carried out under natural conditions.[31-33]

Transcranial Sonography (TCS) is a fundamental non-invasive ultrasonic imaging technique for assessing brain structures. It employs a low-frequency (1-3 MHz) phased-array probe to transmit ultrasound through cranial acoustic windows. By processing the returning echoes from brain tissues, TCS generates 2D or 3D tomographic images of deep brain structures, enabling rapid anatomical visualization. With its short examination time and portable equipment, TCS is particularly suitable for preliminary diagnostics in primary healthcare settings.[34-36]

Electrocorticography (ECoG) requires placing sheet-like electrodes directly on the surface of the cerebral cortex through a craniotomy to collect field potential signals from local neuronal clusters in the cortex. Compared with EEG, ECoG signals avoid signal attenuation caused by the scalp and skull, resulting in a higher signal-to-noise ratio. Its spatial resolution can reach the millimeter level, enabling more accurate reflection of the electrical activity in cortical functional areas.[37,38]

Epidural Electroencephalography (EpiEEG) is a semi-invasive electrical signal sensing technology. Electrodes are placed in the epidural space, without the need to penetrate the dura mater - they can be implanted merely through a skull drilling procedure. Compared with ECoG, EpiEEG causes less damage to brain tissue and carries a lower risk of post-operative infection. Compared with EEG, EpiEEG signals are less interfered by the scalp and skull, have a higher signal-to-noise ratio, and can capture clearer cortical electrical activity. However, since the electrodes are located in the epidural space, the signals are still slightly attenuated by the dura mater, resulting in a spatial resolution slightly lower than that of ECoG.[39]

Stereoelectroencephalography (sEEG) uses stereotactic technology to implant thin needle-like electrodes into deep brain structures or subcortical regions, enabling three-dimensional spatial recording of electrical activity in deep brain areas. Compared with ECoG, sEEG has the advantage of being able to record deep brain regions that are inaccessible to traditional ECoG; it is particularly suitable for localizing epileptic foci originating from deep brain areas or multifocal regions. Meanwhile, sEEG electrode implantation adopts a minimally invasive drilling method, which causes significantly less surgical trauma than ECoG, allows for faster post-operative recovery, and has a lower risk of complications.[40]

Microelectrode array (MEA) is a fundamental invasive neural sensing technology for intracortical recording. It comprises a grid of multiple microscopic electrodes (with tip diameters typically on the micron scale) that are penetrated into the cerebral cortex to capture single-unit activity (SUA) or multi-unit activity (MUA) from individual or small populations of neurons in close proximity. Unlike ECoG which records summed field potentials, MEA enables the direct measurement of action potentials (spikes) with extremely high fidelity. This provides unparalleled resolution for investigating neural coding, microcircuit dynamics, and the firing patterns of specific cell types. The primary limitations include the increased risk of tissue damage and inflammatory response due to cortical penetration, which can lead to signal degradation over time. Furthermore, the recording scope is typically confined to a localized cortical volume immediately surrounding the implant. Recent advancements focus on developing high-density, flexible, and biocompatible arrays to minimize damage and improve long-term stability.[41]

In addition to the above-mentioned technologies, the application of optical technology in brain-computer interfaces is also developing rapidly. Two-photon calcium imaging (2P-Ca^{2+}) is an optical neural recording modality that uses near-infrared femtosecond lasers and genetically encoded calcium indicators to report population and single-cell activity with cellular and subcellular resolution in vivo. Compared with surface electrophysiology, 2P imaging provides precise spatial mapping across layers and cell types while maintaining relatively deep penetration in scattering tissue. It is well suited for dissecting microcircuit dynamics, dendritic integration, and cell-type-specific computations during behavior. Key limitations include limited field of view per scan, motion sensitivity, and an indirect relationship to spiking due to calcium kinetics, which constrains temporal resolution. Advances in resonant/remote focusing, holographic scan patterns, and volumetric approaches expand throughput and enable near-simultaneous recordings from thousands of neurons.[42,43]

Widefield and miniscope calcium imaging extend optical access to mesoscale circuits and freely moving animals, respectively. Widefield systems capture cortex-wide activity over centimeters with high frame rates, enabling studies of inter-areal coordination and brain-wide state dynamics, though signals mix across depths and cell types. Miniaturized head-mounted microscopes, often coupled to GRIN lenses, bring single-cell calcium imaging into naturalistic behaviors, including social interaction and navigation. These approaches trade cellular specificity or optical sectioning for field of view, portability, and experimental ethology. Continued improvements in

Table 1. Comparison of major neural sensing technologies for brain-computer interface.

Technology	Invasiveness	Signal Modality	Spatial Resolution	Temporal Resolution	Advantages	Limitations	Clinical application
Electroencephalography (EEG)[21-23]	Non-invasive	Electrical	Low (cm)	Very High (ms)	Low cost, portable, excellent temporal resolution	Low spatial resolution, susceptible to noise	Routine clinical practice
High-Density EEG (hdEEG)[24]	Non-invasive	Electrical	Medium (mm)	Very High (ms)	Improved spatial resolution over EEG	More complex setup, still indirect measurement	Specialized clinical practice
Magnetoencephalography (MEG)[25]	Non-invasive	Magnetic	High (mm)	Very High (ms)	High spatiotemporal resolution, unaffected by skull	Extremely expensive, bulky equipment	Specialized clinical practice
Functional MRI (fMRI)[26-29]	Non-invasive	Magnetic	Very High (sub-mm)	Low (s)	Excellent spatial resolution, structural & functional imaging	Very low temporal resolution, expensive, immobile	Specialized clinical practice
Functional NIRS (fNIRS)[30-33]	Non-invasive	Optical	Medium (cm)	Low (s)	Portable, safe, usable in natural settings	Limited penetration depth, low temporal resolution	Small-scale clinical practice
Transcranial Sonography (TCS)[34-36]	Non-invasive	Ultrasonic	High (mm)	Low	Portable, rapid, cost-effective	Primarily for structural assessment	Specialized clinical practice
Electrocorticography (ECoG)[37,38]	Invasive	Electrical	High (mm)	Very High (ms)	High SNR, excellent temporal resolution	Requires craniotomy, higher surgical risk	Specialized clinical practice
Epidural EEG (EpiEEG)[39]	Invasive	Electrical	Medium-High	Very High (ms)	Higher SNR than EEG, lower risk than ECoG	Lower resolution than ECoG, signal attenuated by dura	Specialized clinical practice
Stereoelectroencephalography (sEEG)[40]	Invasive	Electrical	High (mm)	Very High (ms)	Records from deep brain structures, minimally invasive	Invasive, limited to targeted regions	Specialized clinical practice
Microelectrode array (MEA)[41]	Invasive	Electrical	Very High (μm)	Very High (ms)	Records single-neuron action potentials, extremely high spatial and temporal resolution	Highest risk of tissue damage, signal stability over time, limited recording volume	Clinical trials
Two-photon calcium imaging (2P-Ca^{2+})[42,43]	Invasive	Optical	Very High (μm)	Medium (tens–hundreds ms)	Cell-type-specific 3D mapping with deep penetration.	Limited field of view, motion sensitivity	Only animal research
Widefield / Miniscope calcium imaging[44,45]	Invasive	Optical	Widefield: mm Miniscope: μm	Medium (tens–hundreds ms)	Free to move around	Depth mixing, motion artifacts	Only animal research
Optogenetics[46]	Invasive	Optical	Very High (μm)	Very high (ms)	Accurate spatio-temporal positioning and low recording artifacts	Requires genetic access	Limited retina trials only

Note: SNR: Signal-to-Noise Ratio.

optics, sensor brightness, and motion-robust registration mitigate photobleaching, scattering, and movement artifacts.[44,45]

Optogenetics enables cell-type-specific, bidirectional optical control of neural circuits by expressing light-gated ion channels or pumps (e.g., ChR2 for excitation, GtACR/Halo variants for inhibition). Compared with electrical stimulation, optogenetics offers genetic targeting, minimal stimulation artifacts in recordings, and precise spatiotemporal patterning, including single-cell activation via holography. Limitations include the need for genetic access, light delivery constraints in deep tissue, and potential heating or phototoxicity at high powers. Emerging red-shifted opsins, micro-LED/optical-fiber implants, and patterned light engines improve depth reach and reduce crosstalk, enabling "all-optical physiology" that combines simultaneous optical readout and stimulation for closed-loop circuit interrogation.[46]

To provide a clearer and more concise comparison of the technical characteristics, advantages, and limitations of the neural sensing technologies discussed above, a systematic summary is presented in Table 1. This table contrasts key attributes such as invasiveness, spatial and temporal resolution, and primary applications, offering a valuable reference for selecting the appropriate technology for specific neuroscience research or brain-computer interface applications.

Neuromodulation technology

Neuromodulation technology is fundamentally centered on deciphering brain mechanisms. By actively intervening in the activity of neurons or the functionality of neural networks, it enables precise regulation of neural functions. It encompasses multimodal approaches such as electrical, magnetic, optical, and ultrasonic stimulation, as well as neurofeedback training, allowing for the selection of appropriate methods based on specific needs.[47,48] The core objectives of this technology are twofold: firstly, to treat neurological and psychiatric disorders through regulating abnormal brain activity and alleviating associated symptoms; and secondly, to enhance cognitive functions—such as attention and memory—by optimizing the connectivity within brain networks. In terms of technical implementation, approaches are categorized based on invasiveness: invasive modulation involves surgical device implantation to enable precise targeted regulation, whereas non-invasive modulation employs external devices to intervene, offering high safety and broad applicability across populations.

Transcranial electrical stimulation (tES) is a non-invasive regulation tech-

nique, which can be classified into subtypes such as transcranial direct current and alternating current stimulation. By applying low-intensity current through scalp electrodes, the intracranial electric field changes the membrane potential of neurons to regulate cortical excitability or brain region rhythm synchronization. Its device weighs only a few hundred grams, is head-mounted, suitable for home use, easy to operate and highly secure. However, the regulation only acts on the superficial layer of the cortex, with low precision and significant individual differences. It can be used to enhance cognitive function, learning ability and neurorehabilitation.[49-51]

Transcranial Direct Current Stimulation (tDCS) is a core technique within the tES family. It applies a weak, constant direct current (typically 1-2 mA) via scalp electrodes to modulate cortical excitability. The mechanism of action involves subthreshold polarization: the anode depolarizes neuronal membranes, increasing the likelihood of spontaneous firing, while the cathode hyperpolarizes them, decreasing their excitability.[52] Its advantages include device simplicity, high safety, excellent tolerability, and the ability to be combined concurrently with cognitive training, making it a highly promising tool for cognitive enhancement and rehabilitation.

Transcranial ultrasound stimulation (tUS) is a non-invasive neuromodulation technique that uses low-intensity pulsed ultrasound waves to modulate neural activity. By focusing ultrasound beams through the skull, tUS can target specific deep brain structures with high spatial precision without the need for surgery. The mechanical pressure exerted by ultrasound waves influences neuronal membrane properties and modulates ion channel activity, thereby altering excitation and inhibition patterns in targeted circuits. Its key advantages include the ability to reach subcortical regions, excellent focal precision, and a favorable safety profile. However, current limitations include the need for precise acoustic calibration, limited long-term safety data, and individual variability in skull transmission affecting efficacy. It shows potential applications in treating neuropsychiatric disorders such as depression and essential tremor, as well as enhancing cognitive functions through network modulation.[53-55]

Transcranial magnetic stimulation (TMS) is a non-invasive regulation technique. It releases a brief strong magnetic field through coils above the scalp, which penetrates the scalp and skull and induces an intracranial current to activate neurons in the target brain region. It is divided into single-pulse TMS and repetitive pulse TMS subtypes. Its regulation is precise, the depth of action reaches the deep cortex, and there is sufficient clinical evidence.[56,57] However, the equipment is large in size, has contraindications for irritation, takes a long time for a single treatment, and requires multiple sessions to show significant effects. It can be used to treat movement disorders, Alzheimer's disease (AD), mild cognitive impairment, epilepsy, multiple sclerosis, sleep disorders and consciousness disorders.[58-60]

Deep Brain Stimulation (DBS) implants fine electrodes into deep brain regions through stereotactic surgery and connects them to a chest pulse generator to release high-frequency electrical stimulation and regulate brain function. Its regulation is deep and accurate, real-time parameter adjustment is possible, the effect is long-lasting and reversible, and it has a wide range of applications. However, the surgical risks are high, the equipment costs are high, there may be side effects, and long-term follow-up is required. It can be used for refractory PD, depression, etc.[61-64]

Electroconvulsive therapy (ECT) is a longstanding and highly effective neuromodulation treatment, primarily reserved for severe, treatment-resistant depression and other major psychiatric disorders. Modern modified ECT is performed under general anesthesia and muscle relaxation. It involves applying a brief, precise electrical stimulus to induce a generalized, seizure-like activity in the brain. This triggers widespread neurochemical and neuroplastic changes, including an upregulation of neurotrophic factors and a reset of dysfunctional brain network connectivity. Despite its associated cognitive side effects, such as transient memory disturbance, it remains the most potent antidepressant intervention available.[65]

Spinal cord stimulation (SCS) is a minimally invasive neuromodulation technique. It involves implanting electrodes in the epidural space of the spinal cord and connecting them to a pulse generator to intervene in neural signal transmission with weak electrical pulses. Its mechanism of action includes blocking pain signals based on gating theory, promoting the release of endogenous opioid substances, and regulating neurotransmitter transmission, etc. It is currently widely used in the treatment of chronic pain such as postherpetic neuralgia and complex regional pain syndrome.[66-70]

Optical neuromodulation is an emerging technique that enables precise control of neural activity through the combination of genetic and optical methods. By introducing light-sensitive ion channels or pumps into specific neuronal populations via viral vectors, neurons can be selectively activated or inhibited using light of defined wavelengths. This approach achieves millisecond temporal precision and cell-type specificity that far exceed those of traditional electrical stimulation. Mechanistically, optogenetic stimulation modulates neural circuits by directly depolarizing or hyperpolarizing targeted neurons, thereby reshaping local and large-scale network dynamics and influencing behavior, perception, or pathological oscillations.[71,72]

Given the diversity in mechanisms, applications, and technical specifications of various neuromodulation technologies, a comparative overview is essential for understanding their respective roles. Table 2 summarizes the key characteristics, advantages, limitations, and primary applications of the major modulation techniques discussed in this chapter, providing a structured reference for their comparative analysis.

SENSORY DISORDERS

Overview of sensory disorders

The sensory system is the fundamental pathway through which humans interact with their external environment. Specialized sensory organs detect external stimuli such as light, sound, odor and pressure, converting them into neural signals that are ultimately integrated into subjective experiences within the cerebral cortex. The major sensory modalities are vision, hearing, olfaction, taste, touch and vestibular function. Each plays a distinct role: vision dominates the acquisition of spatial information, hearing supports the recognition of sound and communication through speech, touch enables interaction with objects and perception of danger, while olfaction and taste contribute to emotion and nutritional intake. The vestibular system, meanwhile, maintains balance and spatial orientation.[73] According to the World Health Organization (WHO), over 2.2 billion people worldwide experience visual impairment, including at least 43 million cases of blindness, while more than 1.5 billion people have varying degrees of hearing loss.[74] Additionally, spinal cord injury and neurodegenerative diseases (e.g., PD) often lead to multisensory dysfunction, particularly in modalities such as touch and olfaction.[75] Conventional treatments, such as pharmacological interventions, can alleviate mild deficits, but are largely ineffective for severe or irreversible impairments, including retinitis pigmentosa and profound deafness.[76] BCI technology offers innovative strategies for diagnosing and treating sensory disorders by establishing direct communication between the brain and external devices,[77,78] as shown in Figure 3.

Visual and auditory restoration

Visual impairment is usually caused by a disruption to the visual signal transmission chain, which can be due to retinal disease, optic nerve injury or cortical dysfunction.[79] Visual BCI offers a revolutionary way to restore functional vision by bypassing the eye or optic nerve and stimulating the visual cortex directly. Non-invasive BCI such as EEG objectively quantifies the integrity and sensitivity of visual pathways by collecting visual evoked potentials, and combines eye tracking to evaluate eye movement and gaze disorders, providing a basis for diagnosis, follow-up, and rehabilitation.[80-82]

Retinal prostheses and cortical implants are two mainstream invasive treatment methods currently available. Retinal prostheses are suitable for patients with partial retinal viability. They convert camera-derived signals into electrical pulses that stimulate residual retinal neurons via electrode arrays. In contrast, cortical implants bypass the retina and optic nerve entirely by stimulating the visual cortex directly to evoke phosphenes, which are perceived patterns of light spots forming the basis of rudimentary vision.[83] Advances in these technologies not only restore light perception, but also enhance sensitivity to color, object contours and the direction of motion of high-contrast objects.[84] MEA enables precise spatiotemporal stimulation. Studies have shown that a 96-channel Utah array can elicit spatially organized phosphene patterns that support basic shape recognition.[85] In the short term, non-invasive BCI is preferred for diagnosis and monitoring, and retinal implants can provide basic visual recovery. In the medium term, it is expected to improve

Table 2. Comparison of major neuromodulation technologies.

Technology	Invasiveness	Advantages	Limitations	Applicati26ons	Clinical application
Transcranial Electrical Stimulation (tES)[49-51]	Non-invasive	Portable, easy to operate, high safety profile, suitable for home use	Limited penetration depth, low spatial precision, significant individual variability	Cognitive enhancement, learning ability, neurorehabilitation	Early clinical and research use
Transcranial Direct Current Stimulation (tDCS)[52]	Non-invasive	Low cost, portable, easy to use, very safe profile; can be combined with other therapies.	Limited focality, subtle effects requiring multiple sessions, sham condition is a challenge	Cognitive enhancement, depression, chronic pain, stroke rehabilitation	Widely used in clinical trials
Transcranial Ultrasound Stimulation (tUS)[53-55]	Non-invasive	Deep penetration, high spatial precision, non-invasive targeting of subcortical structures	Skull transmission variability, requires precise targeting, limited long-term safety data	Depression, essential tremor, cognitive modulation	Early clinical and research use
Transcranial Magnetic Stimulation (TMS)[56-60]	Non-invasive	Good spatial precision, reaches deeper cortical layers, substantial clinical evidence base	Large equipment, seizure risk, long treatment sessions, effects often require multiple sessions	Movement disorders, Alzheimer's disease, epilepsy, depression, sleep disorders	Routine clinical practice
Deep Brain Stimulation (DBS)[61-64]	Invasive	High precision for deep targets, effects are lasting and reversible, parameters are adjustable	High surgical risk, high cost, potential for side effects, requires long-term clinical follow-up	Refractory Parkinson's disease, depression, essential tremor	Routine clinical practice
Electroconvulsive Therapy (ECT)[65]	Invasive	Most effective for severe depression, rapid onset of action	Cognitive side effects, requires general anesthesia, significant social stigma	Treatment-resistant depression, catatonia, acute suicidal risk	Routine clinical practice
Spinal Cord Stimulation (SCS)[66-70]	Invasive	Effective pain blockade, promotes release of endogenous opioids	Invasive implantation procedure, hardware-related risks	Chronic pain conditions, failed back surgery syndrome, complex regional pain syndrome	Routine clinical practice
Optogenetics (optical neuromodulation)[71,72]	Invasive	Cell-type specificity, millisecond temporal precision, high spatial resolution	Requires genetic modification and surgery, potential tissue heating and phototoxicity	Seizure interruption, Parkinsonian pathway modulation, vision restoration research	Human use limited to pilot retinal studies

recognition accuracy and expand "super vision" capabilities through higher channel electrodes, optimized algorithms, and broadband technology.

Auditory impairment results from disruptions in the auditory pathway, including cochlear damage, auditory nerve injury, or auditory cortex dysfunction.[86] Auditory BCI is being used more and more in clinical and research settings, providing objective tools for diagnosing hearing loss and language disorders by recording brain responses to sound via EEG.[87] These approaches allow clinicians to assess auditory discrimination, music recognition, and speech comprehension in cochlear implant (CI) users, thus evaluating the long-term effectiveness of implantation. For instance, biomarkers such as the P1 component—a positive-going event-related potential that peaks approximately 100 milliseconds after an auditory stimulus, indicating early cortical processing and maturation of the auditory pathway—and mismatch negativity have been recognized as reliable indicators of auditory and cognitive development in CI users.[88] Furthermore, event-related potential (ERP) paradigms reveal that the P300 component—a later positive deflection occurring around 300 milliseconds post-stimulus, which is associated with cognitive functions such as attention allocation and the detection of rare or significant events—is diminished in children with language deficits. This reduction correlates with poorer language and literacy skills, highlighting the clinical utility of auditory BCI for monitoring rehabilitation.[89] Beyond assessment, auditory BCI has been used to study cortical plasticity after cochlear implantation. Studies demonstrate that unilateral hearing loss induces widespread cortical reorganization during development, while long-term CI use can partially reverse this effect; however, late-onset cases remain more challenging.[90] For patients who are unable to benefit from CI due to cochlear or auditory nerve damage, direct auditory cortex stimulation via BCI is a promising alternative for the future.[91] Even more compelling are hybrid approaches that combine BCI with advanced hearing aids. For example, recent Neuralink experiments have shown that AI algorithms can decode neural signals from the auditory cortex in order to reconstruct intended auditory perception. This establishes a closed-loop BCI that could one day provide seamless, biocompatible auditory compensation.[92]

Somatosensory and balance rehabilitation

Tactile dysfunction is most commonly associated with spinal cord injury, peripheral neuropathy and stroke. Spinal cord injury is particularly devastating as it can lead to a complete loss of tactile sensation below the site of the injury.[93] In recent years, artificial somatosensory systems have attracted considerable interest due to their potential to restore tactile function in patients with sensorimotor impairments. BCI and neuroprostheses have been explored as effective tools for delivering artificial tactile feedback. Studies on patients with spinal cord injuries have demonstrated that stimulating the somatosensory cortex with intracortical microstimulation (ICMS) can evoke natural tactile sensations. Notably, biomimetic ICMS patterns produce sensations that are closer to natural touch, while using less electrical charge. This provides a promising foundation for designing neural prostheses with tactile feedback.[94] In patients with complete spinal cord injury, electrode arrays implanted in somatosensory cortical regions corresponding to hand or foot representations can be coupled with external sensors embedded in prosthetic devices to generate virtual touch. Clinical feasibility trials of electrotactile BCI have demonstrated accuracy rates of 70-100%, with ipsilateral EEG channels outperforming contralateral ones. This confirms the clinical potential of top-down somatosensory BCI training.[95] While much progress has been made in restoring touch, proprioception has received less attention. Future bidirectional BCI that integrate both tactile and proprioceptive feedback will be critical for enabling patients to regain more natural motor control.

Postural balance depends on the accurate integration of visual, vestibular and somatosensory information in the central nervous system. Disruption to these pathways, such as cortical ischaemia following a stroke or interruption to sensory transmission following a spinal cord injury, can result in a significant deterioration in balance control.[96] BCI offers a novel approach to balance rehabilitation, establishing direct brain, device communication channels to regulate neural activity or provide real-time sensorimotor feedback. Current

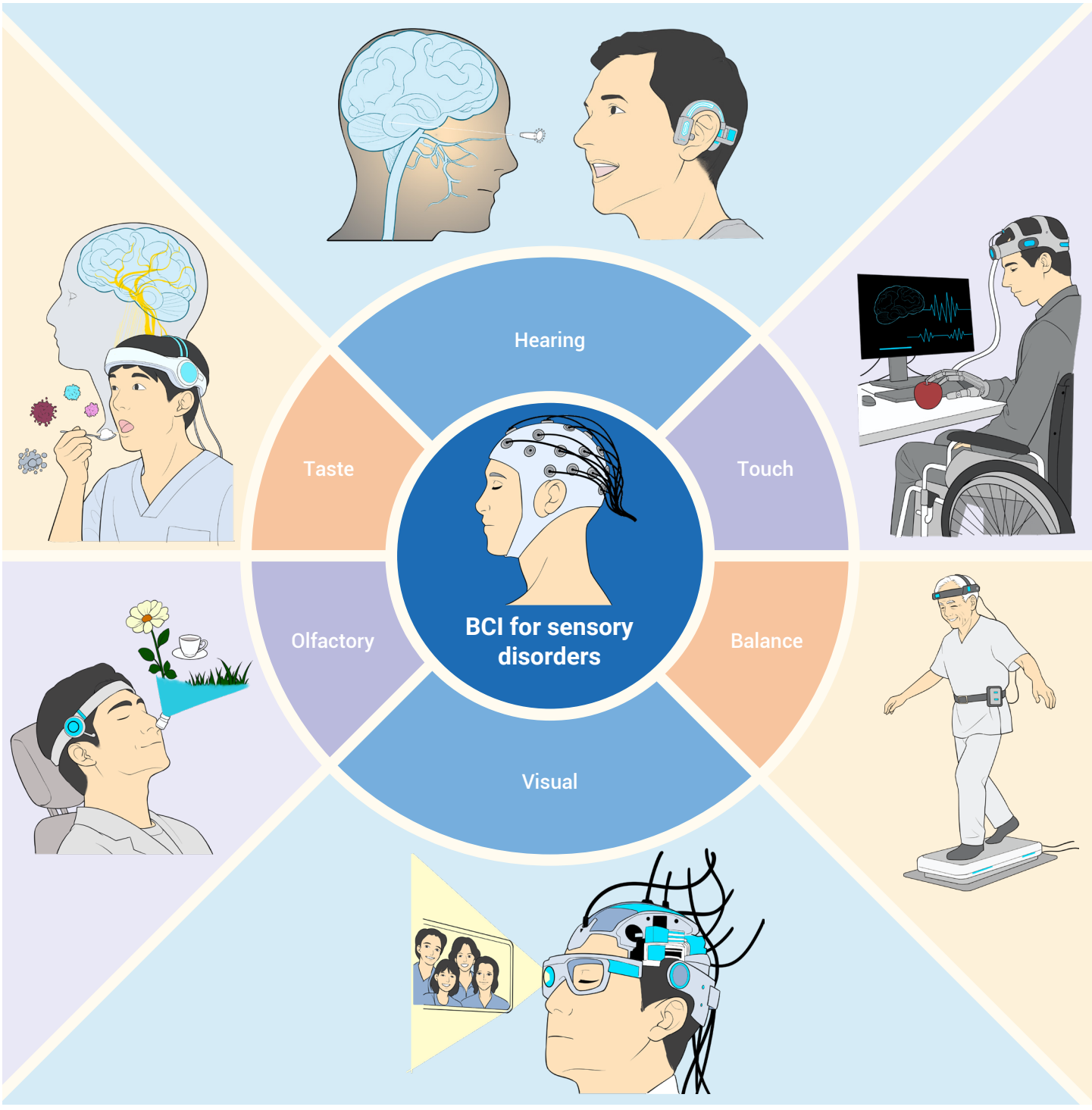


Figure 3. Applications of brain computer interface in sensory disorders.

applications focus on motor imagery training combined with multimodal feedback and the regulation of somatosensory-evoked potentials, as well as integration with functional electrical stimulation (FES). These interventions aim to promote neuroplasticity and sensorimotor reintegration.[97] Clinical studies demonstrate that BCI-based interventions can significantly improve balance in stroke survivors, particularly when combined with FES, as this enhances gait recovery and postural control more effectively than conventional FES alone.[98] However, in severe cases such as complete spinal cord injury or advanced PD, neuromodulation alone is insufficient. In these instances, BCI-FES hybrids offer a centrally driven rehabilitation strategy, directly stimulating muscles while engaging central control pathways. These approaches have shown considerable promise in optimizing neural plasticity, restoring motor and sensory integration, and reallocating cognitive resources for balance recovery.[99]

Olfactory and gustatory function assessment

The integrity of olfactory perception depends on the unimpeded transmission of signals from the olfactory epithelium to the olfactory bulb, piriform cortex and limbic system. Neurological diseases such as PD, AD, stroke and multiple sclerosis often damage these pathways, resulting in hyposmia, anosmia or impaired odor identification.[100] With its ability to record neural signals and modulate brain activity, BCI technology provides an innovative framework for the objective assessment and rehabilitation of olfactory dysfunction.[101] For instance, research indicates that inhaling odors increases

frontal theta activity within 1.5-2.5 seconds, and synchronizing respiratory cycles with this activity enhances decoding performance in olfactory BCI.[102] Paradigms using delayed odor discrimination tasks have achieved accuracies of up to 93.8%, with some participants exhibiting olfactory-related EEG components in the alpha band near C4.[103] These findings confirm that olfactory-related neural activity can be decoded and converted into BCI outputs, paving the way for novel rehabilitation strategies for post-infectious olfactory dysfunction (e.g., following a case of COVID-19) or neurodegenerative diseases. Looking ahead, olfactory BCI may fulfil a triple role by providing objective diagnostic tools, revealing disease mechanisms and supporting rehabilitation through closed-loop systems of neural recording, decoding and regulation.

Taste disorders, which often present as dysgeusia or ageusia, are associated with neurological diseases such as facial paralysis, multiple sclerosis, PD and AD. Despite their importance, BCI studies focusing on taste lag behind those investigating other sensory modalities, primarily due to the diffuse nature of taste receptor pathways and the limited cortical representation of gustation (< 0.1% of the cortical surface). Nevertheless, recent progress in EEG-based decoding has opened up some promising opportunities. Advanced machine learning models using spatiotemporal EEG augmentation and channel-attention convolutional neural networks have achieved remarkable classification accuracies of up to 99.5% for taste decoding.[104] In a therapeutic context, studies have investigated the use of electrical stimulation of lingual or oral mucosal nerves to evoke taste sensations, establishing a link between specific stimulation parameters and the perception of sour, sweet, bitter, salty and umami tastes. More recently, multifunctional gustatory interfaces have been developed, such as a flexible 256-channel tongue electrode system coupled with EEG fusion. This enables preoperative localization of tongue cancer, postoperative monitoring of flap viability and taste decoding in reconstructed tongues, achieving accuracies of up to 97.8%.[105]

Challenges of BCI in sensory disorders

Although BCI has made remarkable progress in addressing sensory system disorders, there are still several key challenges hindering their widespread clinical adoption. Firstly, there are ongoing technical limitations, including low decoding accuracy, reduced perceptual authenticity and limited multimodal integration. Non-invasive BCI suffers from poor signal-to-noise ratios, restricting their ability to detect anything other than basic sensory events (e.g., the presence or absence of a stimulus). Implantable BCIs are more precise but face long-term performance declines due to glial scarring and mismatch between the electrodes and tissue. This leads to a progressive reduction in decoding accuracy of 5-10% annually. Furthermore, most restored sensations are simplified: visual BCI produces only low-resolution phosphenes without color fidelity; auditory BCI struggles with complex sound features, such as timbre; and tactile BCI lacks information about temperature or pain. Secondly, biocompatibility and long-term safety remain pressing concerns. Current electrode materials (e.g., silicon and platinum-iridium) differ mechanically from brain tissue, which can result in immune responses, inflammation and eventual signal degradation. Long-term safety data for implantable sensory prostheses is limited, with most trials reporting follow-up periods of less than five years. Finally, clinical translation faces economic and regulatory barriers. Implantable BCI devices are expensive, far exceeds the financial means of most patients. There are still no standardized guidelines for patient selection, surgical techniques and stimulation parameters, while ethical issues, including data privacy, altered self-perception and the potential misuse of BCI systems for non-medical sensory enhancement, further complicate deployment.

Looking to the future, the next generation of BCIs for sensory disorders is expected to prioritize multimodal integration, closed-loop adaptive systems and enhanced biocompatibility via innovative materials, such as bioresorbable electrodes and nanostructured coatings.[106] Signal decoding will be further enhanced by advances in artificial intelligence and computational neuroscience, enabling more naturalistic and individualized sensory restoration. Addressing these challenges could transform the diagnosis, treatment and rehabilitation of sensory system disorders, ultimately bridging the gap between neurological impairment and functional recovery.

MOTOR DISORDERS

Overview of motor disorders

Motor disorders refer to impairments in motor control caused by abnormalities in the brain, brainstem, spinal cord, or peripheral motor system. Clinical manifestations include bradykinesia, rigidity, tremor, involuntary movements (dyskinesia/dystonia), and gait/postural instability.[107] They can be broadly classified into hypokinetic phenotypes (e.g., PD) and hyperkinetic/mixed phenotypes (e.g., ataxia, chorea, dystonia).

The mechanisms underlying motor disorders are highly heterogeneous, involving neurodegeneration, structural lesions, and functional network abnormalities. Central to these conditions is dysfunction of the cortico–basal ganglia–thalamic–cerebellar–spinal circuits, leading to impaired generation, transmission, and execution of motor commands.[108]

In neurodegenerative diseases, such as PD, its hallmark pathology is the progressive loss of dopaminergic neurons in the substantia nigra pars compacta, disrupting the balance of excitation and inhibition in basal ganglia circuits, and resulting in bradykinesia, rigidity, and resting tremor.[109] Amyotrophic lateral sclerosis (ALS) involves degeneration of upper and lower motor neurons, leading to progressive muscle denervation and paralysis.[110] These disorders are irreversible and progressive, necessitating longitudinal monitoring and adaptive interventions.

Structural lesions such as stroke or spinal cord injury produce motor deficits through acute disruption of motor pathways. Stroke commonly damages the corticospinal tract or basal ganglia, causing contralateral hemiparesis and fine motor impairments.[111] Spinal cord injury interrupts descending motor commands, leading to paraplegia or quadriplegia.[112] Rehabilitation in these patients focuses on exploiting residual pathways or alternative circuits.

In addition, many motor disorders involve abnormal connectivity at the network level. For instance, cerebellar–cortical dysconnectivity is a key mechanism of impaired motor coordination and abnormal postural control in ataxia and dystonia.[113] Stroke and traumatic brain injury also induce widespread network reorganization, which may result in compensatory or maladaptive plasticity, creating both opportunities and uncertainties for rehabilitation outcomes,[114] as show in Figure 4.

Assessment and diagnostic applications of BCI in motor disorders

BCIs decode neural activity to provide objective diagnostic and functional assessment tools for motor disorders with advantages of higher temporal-spatial resolution. EEG is the most widely used modality due to its high temporal resolution and noninvasiveness. In PD, excessive synchronization in the beta band during resting-state EEG allows high-accuracy patient classification using BCI spectral features.[115] In stroke, abnormal event-related desynchronization/synchronization reflects motor cortical damage and correlates with clinical motor deficits.[116] In ALS, reductions in beta-band power have been proposed as biomarkers for longitudinal monitoring.[117]

fNIRS, which captures hemodynamic responses, is resistant to motion artifacts and suitable for bedside and long-term rehabilitation monitoring. Studies have shown aberrant frontal activation in PD during gait tasks and reduced motor cortical oxygenation in stroke, both of which can be captured by fNIRS-BCI for functional evaluation.[118]

fMRI, despite limited real-time utility, provides high spatial resolution to reveal disease-related network abnormalities. Reduced motor network connectivity and impaired dynamic switching have been observed in PD and stroke, correlating with motor impairments. fMRI is thus frequently employed for BCI model training and calibration.[119]

ECoG offers high signal-to-noise ratio and access to high-frequency activity, enabling stable disease phenotyping and longitudinal monitoring. In PD, ECoG reliably detects beta oscillations linked to bradykinesia,[120] while in ALS, changes in gamma activity have been shown to reflect cortical degeneration over months to years, supporting the feasibility of long-term ECoG-BCI use.[121]

More recently, multimodal BCIs integrating EEG, fNIRS, EMG, and inertial measurement units have improved disease classification and functional assessment accuracy. EEG–fNIRS fusion enhances detection of PD gait freezing subtypes, whereas EEG–EMG coupling allows joint assessment of central and peripheral dynamics.[122] With the adoption of deep learning and cross-modal attention mechanisms, multimodal BCIs demonstrate greater

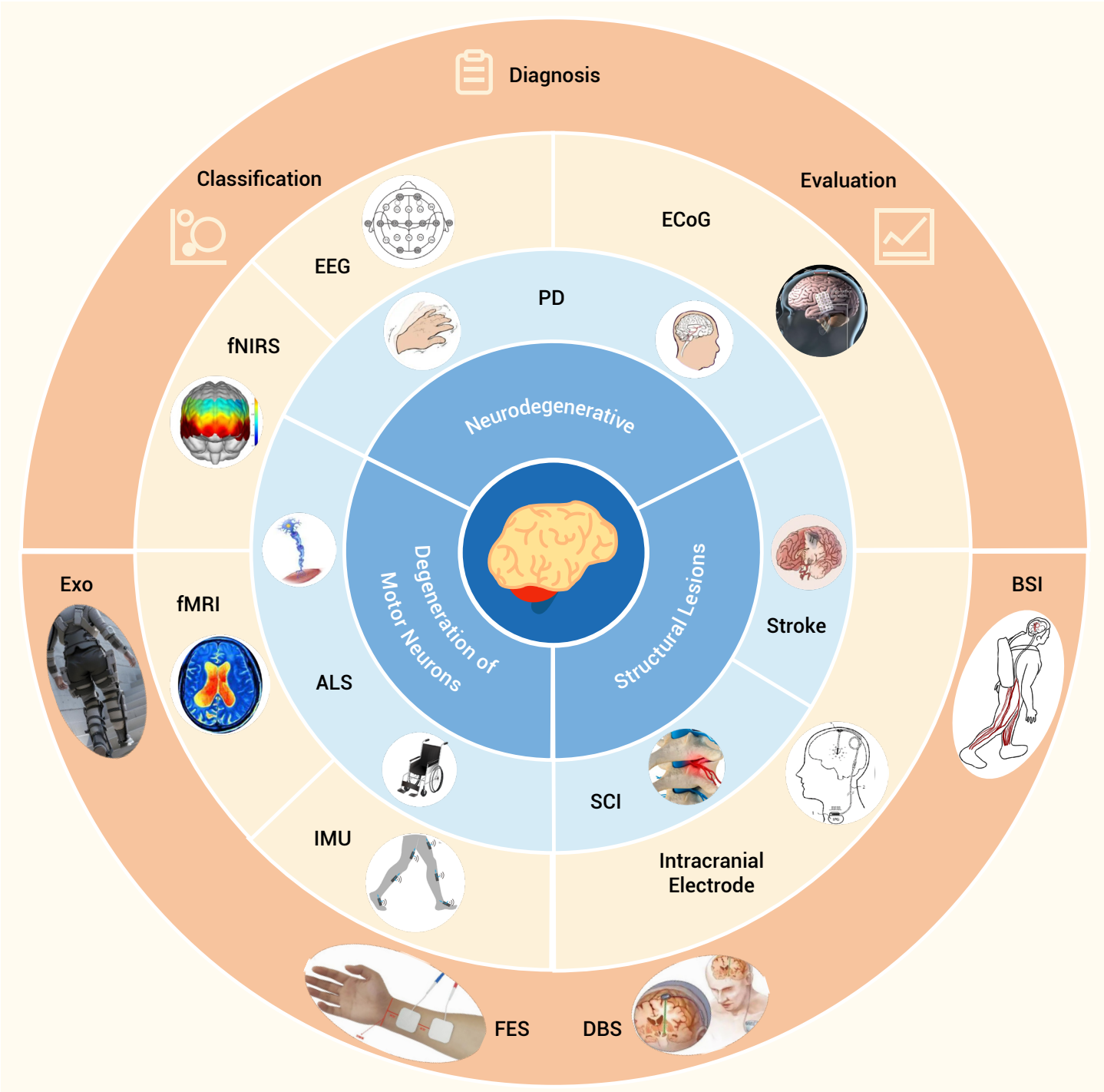


Figure 4. Application of brain computer interface in motor disorders.

robustness in disease classification, severity grading, and prognosis prediction.[123]

Therapeutic and assistive interventions of motor disorders

BCI can not only be used for diagnosis and functional assessment, but also have made progress in functional recovery and rehabilitation based on brain interfaces, from concept validation to clinical feasibility and early efficacy verification.

BCI-FES has achieved landmark clinical evidence in post-stroke upper limb rehabilitation. Randomized controlled trials have shown that FES driven by motor-related cortical activity induces significant and lasting motor recovery, supported by imaging and electrophysiological evidence of enhanced connectivity and cortical reorganization.[124,125]

For spinal cord injury, brain-spine interfaces combining cortical decoding with spatiotemporal epidural electrical stimulation (EES) have enabled real-time restoration of gait and standing in chronic paraplegic patients. Natural walking in ecological environments and residual function after device removal have been reported, suggesting long-term neuroplastic effects.[126,127] In PD, EES may modulate spinal central pattern generators and improve cortico–spinal connectivity, alleviating symptoms such as freezing of gait and postural instability. In stroke, EES could enhance residual cortico–spinal transmission and promote neuroplasticity, thereby supporting motor recovery.

BCI-robot/exoskeleton training enables high-intensity, task-specific rehabilitation. BCI systems synchronize robotic assistance with patient motor intent, improving gait symmetry and endurance. While promising, clinical

translation requires advances in low-latency control, human–robot coordination, and home usability.[128]

Adaptive DBS, a closed-loop approach using neural biomarkers (e.g., beta oscillations), is reshaping treatment paradigms in PD. Early trials demonstrate reduced motor fluctuations, fewer side effects, and prolonged device life compared to conventional DBS.[129,130] Beyond PD, closed-loop stimulation strategies are also being explored in stroke, where real-time cortical or subcortical signals can guide targeted stimulation to enhance motor network reorganization and facilitate functional recovery.

Emerging non-invasive or minimally invasive approaches such as functional ultrasound (fUS), focused ultrasound stimulation, and non-invasive brain stimulation techniques such as tES and tDCS are being explored as complementary read/write pathways. Human studies have demonstrated fUS-based high-resolution decoding and focused ultrasound-based neuromodulation, though larger multicenter trials are needed to confirm safety and reproducibility.[131] Importantly, non-invasive neuromodulation is increasingly viewed as a critical step toward the development of closed-loop systems, as it allows brain activity to be decoded in real time while simultaneously delivering adaptive stimulation. The integration of neural monitoring with precise modulation enables techniques like tES, tDCS, and focused ultrasound to offer safer, more accessible alternatives to invasive devices. This significantly broadens the applicability of closed-loop BCI therapies for movement disorders and neurorehabilitation.

Challenges of BCI in motor disorders

Despite considerable advances in the application of BCI technology to motor disorders, several disorder-specific challenges impede its broader clinical implementation. A major obstacle stems from the inherent characteristics of impaired motor networks, such as pathological synchronization in PD or erratic cortical activity in hyperkinetic disorders, which complicate the accurate decoding of movement intention. These signals are often non-stationary and contaminated by abnormal involuntary movements, reducing the reliability of control commands for assistive or rehabilitative devices. Furthermore, the progressive nature of many neurological conditions means that decoding models can become obsolete as neural reorganization occurs, necessitating frequent recalibration and adaptive machine learning strategies to maintain performance over time.[132]

From a clinical perspective, the heterogeneity of motor impairments across different disorders presents a significant challenge. BCI devices developed for stroke-related hemiparesis may not generalize to gait freezing in PD or loss of motor function in ALS, requiring highly individualized approaches to both signal interpretation and intervention delivery. Another critical issue is the gap between laboratory demonstration and real-world utility: while many systems successfully restore basic motor tasks in controlled environments, they often fail to translate into improved activities of daily living. This may be due to insufficient decoding granularity for complex movements, lack of adaptive feedback in dynamic settings, or limited integration with residual motor function.[133]

Ethical and practical considerations further complicate the deployment of BCI technology in motor disorders. Devices must be usable by individuals who may have accompanying cognitive deficits, spasticity, or fatigue, which affects interaction consistency. Moreover, the high cost and technical support requirements of current systems raise concerns about equity and access, particularly for patients with progressive disabilities who would benefit from long-term use. Addressing these challenges will require not only engineering innovations in robust decoding and adaptive closed-loop control but also larger longitudinal studies to establish clinically meaningful outcomes and validate real-world efficacy in diverse patient populations.

COGNITIVE DISORDERS

Overview of cognitive disorders

The WHO estimates that 1 billion people were over the age of 60 in 2020, and that this age category will double to 2.1 billion people by 2050. Due to the aging of the world population and the lack of available diagnosis and therapies, dementia has emerged as one of the top public health challenges and a major cause of disability and dependency among older people globally. The term "dementia" describes a syndrome of decline in several cognitive domains, i.e., memory, thinking, and the ability to perform daily activities, which will ultimately be severe enough to interfere with independent living. The number of people living with dementia is expected to rise from 55 million in 2019 to 139 million in 2050, according to the WHO.[134] Dementia has physical, psychological, social, and economic impacts, not only for people living with dementia, but also for their families and society at large. In 2019, dementia cost economies globally $1.3 trillion, and it is expected to reach $2.8 trillion by 2030. Age is the most important risk factor for developing dementia. Although the illness gets worse over time, not all people will develop it as they age. Furthermore, gender, genetic factors, hypertension, diabetes, obesity, and living habits also influence the progression of dementia.[135] The most common form of dementia is AD, which accounts for about 60-70% of the cases. Other forms of dementia include vascular dementia (VaD), dementia with Lewy bodies (DLB), frontotemporal dementia (FTD), and Secondary dementia.[136] The boundaries between different forms of dementia are indistinct, and mixed forms often co-exist, which poses significant problems for the diagnosis and treatment of the disease. As elaborated above, both the diagnosis and the development of novel therapeutic strategies remain urgent for dementia. Appropriate diagnosis and treatment of dementia is guided by the cause of dementia and the stage classified by the biological and behavioral symptoms, based on the AT(N) schema proposed by the National Institute on Aging and Alzheimer's Association for AD.[137] Recently, the diagnosis framework has included incorporation of cognitive scales, plasma biomarkers, imaging biomarkers, and EEG analysis. Dubois et al. have highlighted that conventional diagnostics suffer from delays, high biomarker variability, limited imaging sensitivity, and results affected by multiple variables.[138] BCI technology facilitates early diagnosis by capturing and analyzing EEG signals to identify early neural activity changes, and symptom relief through neural modulation techniques, including neurofeedback training that adjusts brain electrical activity, as show in Figure 5.

EEG-based BCI frameworks for cognitive disorders detection

BCI technology acquires and analyzes neuro-electrophysiological signals or neuroimaging data to provide a non-invasive, high spatiotemporal resolution approach for the early diagnosis, subtype differentiation, and longitudinal monitoring of dementia. In recent years, EEG-based BCI systems, as well as multimodal frameworks that integrate EEG with fMRI and positron-emission tomography (PET), have demonstrated exceptional promise in identifying specific biomarkers, constructing diagnostic models, and predicting disease progression. These advances are gradually establishing BCI as a pivotal research direction for early recognition and phenotypic stratification of cognitive disorders, offering novel technological support to enhance diagnostic sensitivity and enable precision subtyping in clinical practice.

EEG-based BCI frameworks—by virtue of their high temporal resolution, low cost, and ease of acquisition—have become the principal vehicle for current neuro-electrophysiological investigations of cognitive disorders. Both resting-state and task-evoked EEG features exhibit robust discriminative capacity for identifying mild cognitive impairment (MCI) and AD. A substantial body of literature has demonstrated that, relative to healthy older adults, AD patients exhibit increased power in slow-frequency bands (delta and theta) and decreased power in fast-frequency bands (alpha and beta).[139-141] By decomposing resting-state EEG into periodic and aperiodic constituents, subsequent work has further revealed that the observed spectral alterations in AD are driven exclusively by changes in the periodic component, with no concomitant modification of aperiodic activity.[142] These findings indicate that disrupted oscillatory synchronization may constitute an early electrophysiological signature of AD. Large-scale cohort studies have further corroborated the robustness and biological validity of EEG-BCI frameworks for AD detection. Leveraging a sample of 890 participants, Jiao et al. showed that occipital-parietal theta power and Hjorth complexity accurately discriminate healthy controls (HC) from individuals with mild cognitive impairment or Alzheimer's disease, and correlate significantly with CSF Aβ/tau biomarkers.[143] Under cognitive challenge, patients with MCI and AD exhibit task-specific spectral and connectivity anomalies. Han et al. reported that, relative to HC, patients with mild AD displayed elevated alpha power during the encoding phase and increased theta and alpha power during the retrieval phase of an object-location memory task.[144] During visuospatial paradigms, individuals across the

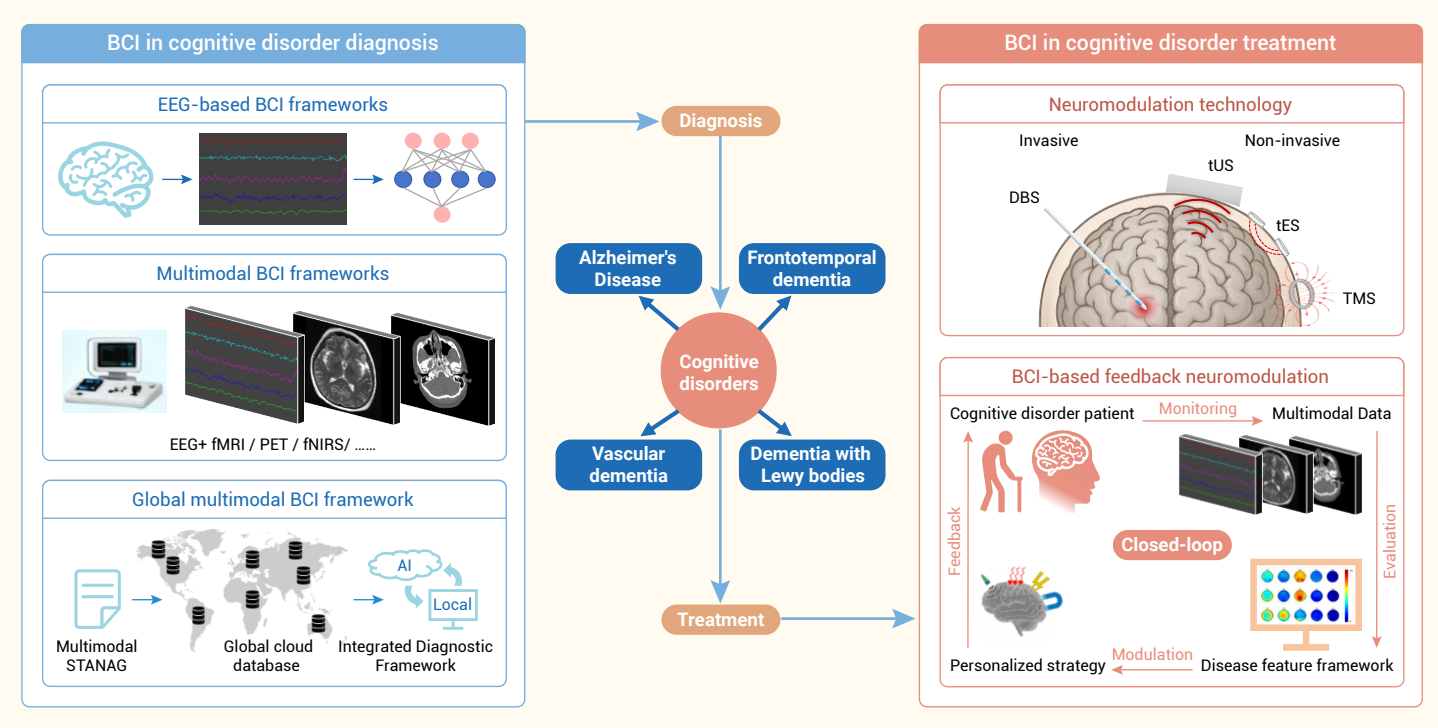


Figure 5. Application of brain computer interface in cognitive disorders.

AD spectrum exhibit attenuated occipital alpha oscillations alongside enhanced gamma power, and these deviations correlate robustly with mini-mental state examination scores.[145] ERP analyses further revealed prolonged latencies and reduced amplitudes of P300 and N200 components in MCI and AD cohorts during N-back working-memory tasks. Exploiting these features, Fraga et al. constructed a classifier that achieved high accuracy in ternary discrimination among HC, MCI, and AD.[146]

EEG-based BCIs not only detect the presence of cognitive impairment but also discriminate among distinct neurodegenerative diseases. Relative to FTD, AD is characterized by markedly stronger delta–alpha and delta–beta phase-amplitude coupling.[147] In contrast, FTD patients show elevated Hjorth complexity over frontal-temporal regions, with significantly higher signal amplitude and nonlinear irregularity. When combined with spectral divergence across parietal and occipital cortices, these features support high-accuracy classification of AD versus FTD.[148] In DLB, EEG-BCIs reveal a prominent slow-wave enhancement that is topographically maximal over occipital and parieto-occipital areas. The magnitude of delta power increase correlates positively with core DLB clinical manifestations, including visual hallucinations and rapid-eye-movement sleep behavior disorder.[149] In summary, pure EEG-based BCI frameworks offer a non-invasive, efficient, low-cost, and highly reliable approach for the diagnosis and differential diagnosis of cognitive disorders. Although pure EEG-BCIs have demonstrated commendable performance in disease detection and progression forecasting, their inherently limited spatial resolution and insufficient capacity have prompted researchers to integrate EEG data with structural, metabolic, or hemodynamic neuroimaging.

Multimodal BCI frameworks for cognitive disorders detection

This strategy has given rise to a new generation of multimodal BCI diagnostic systems. Centered on the complementarity of electrophysiology and imaging, the framework leverages millisecond-level neurodynamics from EEG while fMRI, PET, or structural MRI supply millimeter-level spatial localization and pathometabolic signatures. The confluence preserves high temporal resolution and, simultaneously, enables a unified characterization of whole-brain function, structure, and metabolism.

Brueggen and colleagues first applied simultaneous resting-state EEG-fMRI to patients with mild AD, demonstrating a marked attenuation of the positive correlation between alpha power and blood-oxygen-level-dependent (BOLD) signal within the default mode network, thalamus, and other regions in the AD cohort.[150] Using concurrent resting-state EEG-fNIRS, researchers observed significant neurovascular decoupling in mild AD, manifesting as weakened coupling of theta oscillations with oxy-hemoglobin and of alpha oscillations with deoxy-hemoglobin, compared with unimodal features. These multimodal neurovascular coupling indices achieved superior discrimination between AD and controls.[151] Colloby et al. further integrated a resting-state EEG classifier with medial temporal lobe atrophy scores to construct an EEG-MRI fusion model that attained 90% overall accuracy for differential diagnosis of AD versus dementia with Lewy bodies (93% specificity for AD, 86% sensitivity for DLB).[152] Collectively, multimodal BCI frameworks overcome the spatial constraints of EEG-based BCI, significantly outperform single-modality approaches, and exhibit strong potential as adjunctive diagnostic tools. In recent years, the establishment of multicenter data-sharing platforms—such as the Alzheimer's Disease Neuroimaging Initiative and the National Alzheimer's Coordinating Center—has catalyzed a shift toward large-scale, multimodal modeling.[153] BCI technology, particularly synergistic frameworks that integrate EEG with multimodal neuroimaging, blood biomarkers, and genomic data, is now providing an unprecedented technical platform for the early detection, subtype differentiation, and longitudinal monitoring of neurodegenerative cognitive disorders. With ongoing advances in standardized multimodal data acquisition, enhanced model interpretability, and miniaturized hardware, BCI is poised to become a cornerstone technology for large-scale screening, precision phenotyping, and therapeutic-efficacy assessment in cognitive impairment.

Applications of BCI for treatment of cognitive disorders

A growing amount of research has been focusing on the treatment of cognitive disorders. Cholinesterase inhibitors such as donepezil, and N-methyl-D-aspartate (NMDA) receptor antagonist memantine can help manage the dementia symptoms, but have little effect on the dementia progression and patient prognosis. CIs inhibit the hydrolysis of acetylcholine to increase the acetylcholine level in the synaptic cleft,[154] and NMDA receptor antagonists reduce the excitotoxicity of Glutamate to alleviate neuron damage.[155] Recent progress has been made in the development and approval of disease-modifying therapies, including Lecanemab,[156] Donanemab,[157] and Aducanumab.[158] Those novel monoclonal antibodies could reduce brain amyloid burdens and are associated with a moderately less decline on clinical

measures of cognition in early dementia, but fail to stop dementia progression or significantly improve cognitive function. As AD progresses to severe stages, pharmacological treatments become less effective, patients suffer from physiological dysfunction and neuropsychiatric symptoms, and the societal and economic burden increases. Multidrug therapies are often necessary but can result in drug interactions and increased side effects, complicating care for patients with compromised liver and kidney functions.

Beyond pharmacological interventions, applying physical neuromodulation methods such as acoustic, optical, electrical, and magnetic stimulation—whether invasively or non-invasively—to the targeted brain of dementia patients represents another pathway that researchers are exploring. DBS involves implanting electrodes within areas of the brain, which is a potential therapeutic approach for severe dementia. Researchers found that the nucleus basalis of Meynert.[159] the fornix,[160] and the ventral striatum DBS[161] effectively improved the cognitive function in AD patients.[162] However, the clinical application of DBS is limited by the possible side effects and painful nature of the invasive approaches. Noninvasive brain stimulation (NIBS), including TMS, tUS, and tES, is gradually emerging as a promising approach in the treatment of dementia.[163] Most studies have shown that dementia disorders tend to correlate with functional connectivity alterations in the whole brain circuits rather than in a specific local region,[164] corresponding to this, NIBS techniques alter connectivity in both targeted and remote brain regions. Mencarelli and colleagues' preliminary results supported the possibility of using TMS targeting the precuneus to arrest brain atrophy progression by manipulating network connectivity patterns in patients with mild-to-moderate AD.[165] Dhaynaut and colleagues found that bilateral temporal lobes tES seems to induce gamma activity and observed a possible effect on brain protein clearance in mild-to-moderate AD patients.[166] Beisterner's study found that tUS significant improvement of neuropsychological function correlated with an upregulation of the memory network.[167] NIBS effects seem to be activity-dependent since they are notably enhanced and reinforced when combined with cognitive and behavioral activities to promote enduring outcomes. Considering the complex and heterogeneous substrate of dementia, involving a cascade of causative factors, it is unlikely that a single therapeutic approach may be sufficient and satisfactory to treat cognitive decline. Therefore, NIBS techniques have increasingly been applied as single or add-on therapies (i.e., combined with pharmacological drugs or cognitive training) for people suffering from dementia.[168]

Recent years, numerous studies have also explored the potential application of BCI technologies in rehabilitation and cognitive neuroscience. BCI methods detect brain signals in real time, converting them into commands to control external devices, or translating external stimuli into signals that the brain can perceive.[169] For example, neurofeedback training measured and analyzed brainwaves of a participant to give auditory and visual stimuli, which could inhibit the undesirable brain activity and regulate the brain for the better. Several studies have been proposed in patients with mild cognitive impairment and AD patients and showed significant improvement in cognitive function, positing this approach as a novel direction for non-pharmacological AD treatment.[170] Additionally, BCI can be integrated with other therapeutic interventions like TMS and electrical stimulation to amplify the therapeutic outcomes in Lock-in syndrome[171] and epilepsy,[172] but these combinations have not been used in patients with dementia. Indeed, controlling and modulating EEG brain activity to induce neuroplasticity is a key aim of BCI applications in NIBS methodologies.

Challenges of BCI in cognitive disorders

Despite the promising applications of BCI in cognitive disorders, several challenges impede its widespread clinical adoption. A primary obstacle lies in the inherent variability of brain signals among individuals, particularly in aging populations with neurodegenerative conditions. Factors such as differing disease etiology, severity, medication effects, and individual anatomical differences contribute to significant heterogeneity in electrophysiological patterns. This variability complicates the development of standardized biomarkers and robust classification models that generalize across diverse patient groups. Moreover, cognitive disorders often involve diffuse brain alterations rather than focal abnormalities, making it difficult to identify specific and reliable neural signatures for accurate diagnosis and monitoring.

Another challenge is the practical implementation of BCI systems in cognitively impaired populations. Patients with dementia may struggle with compliance, attention, and task engagement during EEG or neuroimaging recordings, leading to increased noise and artifacts in the data. The cognitive effort required for some paradigms—especially task-based EEG measurements—might be overwhelming for patients, thereby affecting data quality and interpretability. Furthermore, the progressive nature of disorders like AD means that signal features may evolve over time, necessitate adaptive models and continuous recalibration, which poses additional technical and logistical burdens.

Finally, the translation of BCI technology from research settings to clinical practice faces methodological and regulatory hurdles. Many current findings are based on relatively small, single-center studies, raising concerns about reproducibility and generalizability. The lack of large-scale validation and standardized protocols limits the comparability of results across studies. Additionally, the integration of multimodal data—while promising—introduces complexity in data fusion, interpretation, and ethical considerations related to data privacy and patient consent. For BCI to become a mainstream tool in cognitive disorders, these challenges must be addressed through collaborative efforts integrating clinical, technical, and regulatory perspectives.

MENTAL DISORDERS

Overview of mental disorders

Mental disorders represent a major global health challenge,[173] with high prevalence and profound disability caused by conditions such as depression,[174] bipolar disorder,[175] schizophrenia,[176] and substance use disorder.[177] Yet their management remains suboptimal: diagnosis still relies largely on subjective symptom reports and clinical interviews,[178] and treatment is often based on trial-and-error pharmacotherapy or empirical neuromodulation (e.g., TMS, ECT).[179,180] This approach fails to account for the marked heterogeneity in symptoms, biology, and treatment response, leading to misdiagnosis, resistance, and significant societal costs.[181]

Against this backdrop, there is an urgent demand for precise diagnostic and treatment strategies grounded in individual physiological data such as biomarkers and neuroimaging.[182,183] BCI technology offers a promising avenue: by integrating high-temporal-resolution brain signals (e.g., EEG, fNIRS) with multimodal clinical and molecular data, and applying machine learning, BCI can identify patient-specific circuit dysfunctions, providing objective markers for diagnosis, subtyping, and prognosis.[184,185] Beyond diagnostics, BCIs also pave the way toward closed-loop therapeutic systems capable of decoding brain states in real time and adaptively guiding interventions such as DBS or TMS.[186-188] Ultimately, this enables truly tailored and dynamically optimized precision therapy for each patient, as show in Figure 6.

Diagnosis of mental disorders using BCI

Beyond their immediate application in improving diagnostic accuracy, a profound implication of BCIs lies in their potential to redefine the neurobiological taxonomy of psychiatric disorders. The symptom-based diagnostic categories in current clinical practice, while essential for communication, encompass vast underlying neurobiological heterogeneity.[189] This heterogeneity is a major confound in psychiatric research, diluting effect sizes in clinical trials and obfuscating the search for mechanistic pathways. BCI-derived biotypes aim to deconstruct these traditional syndromes into more homogeneous subgroups based on shared neurophysiological signatures, such as specific patterns of aberrant oscillatory activity or functional connectivity.

Crucially, these data-driven biotypes may cut across conventional diagnostic boundaries (e.g., defining a 'reward circuit deficiency' biotype that includes patients with both negative symptom schizophrenia and anhedonic depression). By stratifying patients based on mechanism rather than symptom, BCI research provides a foundational framework for future studies. It enables a more precise mapping between pathophysiological mechanisms and therapeutic interventions, ultimately facilitating the development of targeted treatments for neurobiologically defined patient subgroups and accelerating the pace of discovery in psychiatric neuroscience.

Schizophrenia is a chronic and disabling psychiatric disorder affecting about 1% of the population, characterized by heterogeneous symptoms

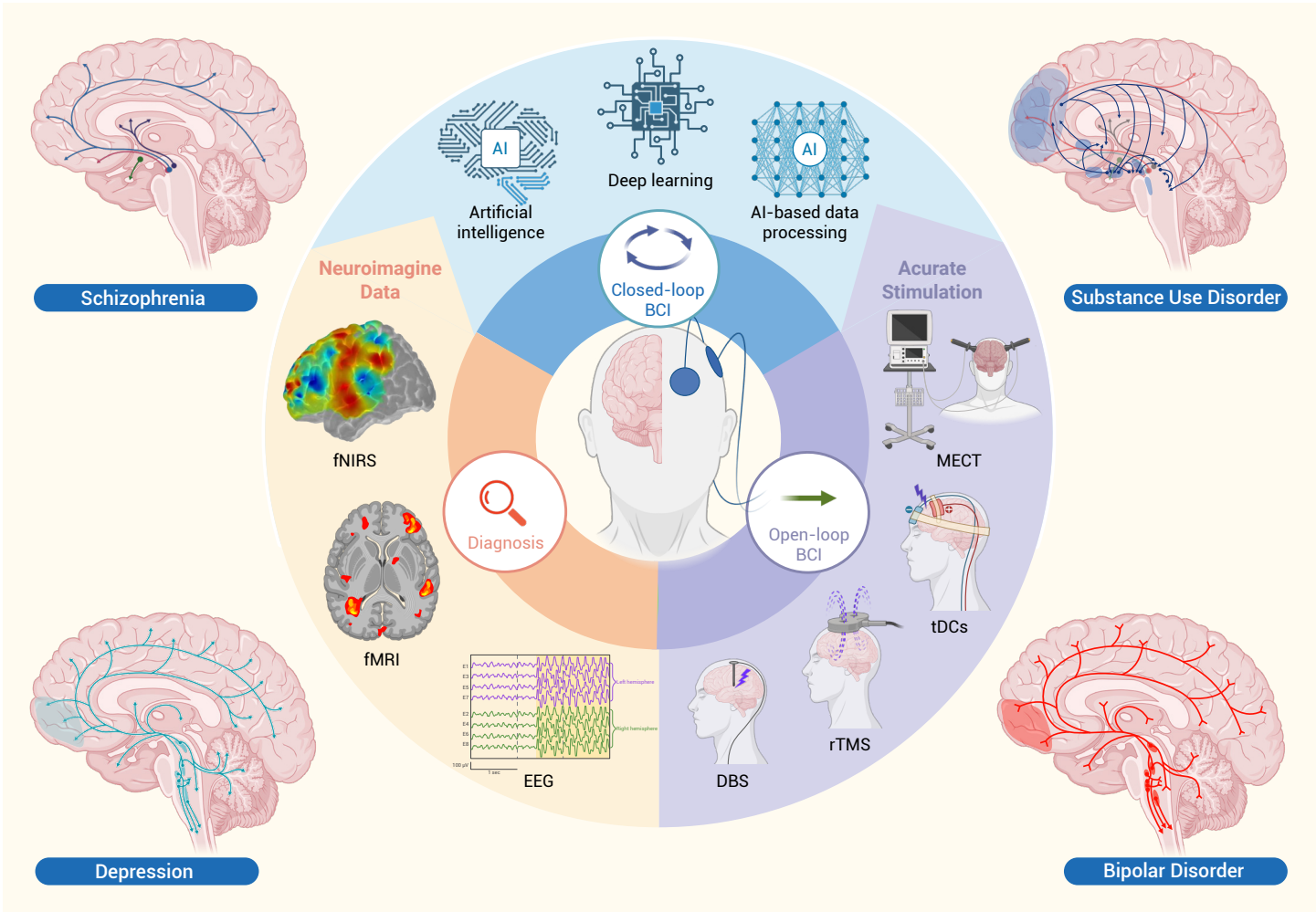


Figure 6. Application of brain computer interface in mental disorders.

spanning positive (hallucinations, delusions), negative (blunted affect, avolition), and cognitive domains (working memory, executive deficits).[190-192] Neurobiological models highlight dopaminergic dysregulation—hyperactivity in mesolimbic circuits linked to positive symptoms and hypoactivity in mesocortical pathways contributing to negative and cognitive impairments.[193,194] The glutamate hypothesis further implicates NMDA receptor hypofunction as an upstream mechanism that disrupts dopamine signaling.[195] In parallel, neurodevelopmental models suggest aberrant synaptic pruning during adolescence undermines cortical maturation, consistent with neuroimaging findings of widespread dysconnectivity involving the prefrontal cortex, temporal regions, hippocampus, and thalamus.[196]

These alterations in brain connectivity are critically associated with the emergence of core symptoms such as hallucinations, delusions, and cognitive deficits. This complex and multifaceted pathophysiology underscores the limitations of current symptom-based diagnostic approaches and highlights the urgent need for objective biomarkers. In this context, BCI technology, capable of capturing aberrant neural circuitry dynamics, offers a promising pathway for refining diagnosis and identifying biologically grounded subtypes.

Recent advances in machine learning and deep learning have markedly improved the neurobiological characterization and diagnostic classification of schizophrenia. Functional connectivity–based deep learning models now achieve high accuracies by capturing disruptions across cortical–striatal–cerebellar circuits and abnormal interactions among default, salience, and control networks.[197] Time-series approaches such as recurrent neural networks further highlight the discriminative role of the dorsal striatum and cerebellum, yielding robust classification performance.[198] Dynamic functional connectivity analyses and temporal graph convolutional networks outperform static methods, revealing state-specific abnormalities in delta, theta, and gamma bands as well as left frontal dysfunction, with particularly strong predictive accuracies.[199,200]

Beyond fMRI, structural connectome studies reveal both shared and disorder-specific network changes across schizophrenia, bipolar disorder, and major depression,[201] while interpretable graph neural networks applied to EEG demonstrate robust cross-site generalizability, identifying theta and alpha power as reliable biomarkers.[202] Prospective EEG-based deep learning approaches have also enabled early risk detection in children, underscoring their translational value for preventive psychiatry.[203] Still, the dissociation between neuroanatomical and symptomatic subtypes highlights persistent biological heterogeneity, reinforcing the need for BCI approaches that integrate multimodal signals with interpretable models.[204]

Mood disorders, including major depressive disorder (MDD) and bipolar disorder (BD), share overlapping depressive symptoms yet differ fundamentally in their neurobiology and clinical management. While both present with episodes of low mood and anhedonia,[205] BD is further defined by recurrent mania or hypomania, and its treatment requires mood stabilizers to avoid antidepressant-induced switching. Given this clinical overlap but divergent treatment needs, reliable biomarkers—particularly neuroimaging signatures distinguishing MDD and BD—are critical for accurate differential diagnosis and safe, effective intervention.[206]

Large-scale neuroimaging studies suggest that MDD is associated with specific alterations in whole-brain functional and structural connectivity, though their utility as diagnostic biomarkers is limited by marked heterogeneity. Resting-state fMRI analyses from multicenter consortia (e.g., REST-meta-MDD, PsyMRI) achieved only modest classification accuracy (~61%) in distinguishing MDD from healthy controls, largely driven by thalamic hyperconnectivity, with most other connections showing mild weakening.[207] Dynamic functional connectivity analyses further reveal increased temporal

variability between the medial prefrontal cortex, insula, and dorsolateral prefrontal cortex, correlating with depression severity and rumination.[208] Structural covariance studies show abnormal topological properties, including increased global efficiency and altered nodal centrality in default mode and thalamo-insular circuits, linked to symptom severity.[209] Importantly, algorithmic harmonization has improved cross-site generalization of rs-fMRI classifiers to ~70%, marking progress toward clinical utility.[210] Collectively, these findings highlight the heterogeneity of MDD and support a shift from categorical classification to dimensional imaging endophenotypes aimed at parsing neurobiological subtypes.[211]

In BD, neuroimaging has identified more distinct and reliable alterations. Structural MRI studies consistently show reduced volumes in the hippocampus, amygdala, and insula, enabling accurate classification across heterogeneous cohorts.[212] Functionally, BD is characterized by limbic–frontal hyperconnectivity (e.g., amygdala–OFC), often contrasting with the connectivity profiles observed in MDD.[213] These abnormalities appear early, even in at-risk youth, as altered default mode network topology and increased frontal efficiency.[214] Multimodal approaches integrating structural and diffusion data further enhance diagnostic precision,[215] while connectome-based models predict future mood symptom severity.[216] Together, these findings suggest that BD is associated with a quantifiable and clinically relevant neuroimaging profile, supporting the development of objective diagnostic tools and personalized treatment strategies.

Substance use disorder (SUD) is increasingly recognized as a chronic and relapsing brain disease characterized by compulsive drug seeking and use despite severe adverse consequences. Clinically, SUD is often conceptualized within a three-stage cycle: (1) binge/intoxication, in which acute reward drives excessive drug consumption;[217] (2) withdrawal/negative affect, dominated by dysphoria, anxiety, and anhedonia upon cessation;[218] and (3) preoccupation/anticipation (craving), defined by obsessive drug-related thoughts and heightened relapse risk. Among these, the craving stage plays a pivotal role, as it is the strongest predictor of relapse and a primary focus for diagnostic and therapeutic innovation.

The neuropathology of SUD involves dysregulation across reward, stress, and executive control networks.[219] Substances hijack the mesolimbic dopaminergic pathway, producing supraphysiological dopamine release in the nucleus accumbens that reinforces drug-taking behavior.[220] With chronic use, neuroadaptations induce a hypodopaminergic state during withdrawal, fueling negative affect and drug seeking.[221] In parallel, glutamatergic dysfunction in prefrontal and orbitofrontal cortices compromises executive control and enhances impulsivity,[222] while cortico-striatal-thalamic circuits reinforce maladaptive habits,[223] These alterations create a self-perpetuating cycle, making craving a quantifiable window into the underlying pathophysiology.[224]

Research on SUD has identified several neural and behavioral predictors of craving and relapse. In cocaine addiction, EEG studies show that cue-induced late positive potential follows a parabolic trajectory during abstinence, peaking at one and six months, while subjective craving decreases linearly—suggesting that neurophysiological signals may capture relapse risk more reliably than self-report (Incubation of Cue-Induced Craving in Adults Addicted to Cocaine Measured by EEG).[225] Beyond substance-specific findings, connectome-based predictive modeling (CPM) has identified a transdiagnostic "craving network" across salience, subcortical, and default mode regions, generalizing across both substance-induced and fasting-induced craving states. CPM has also been applied to predict treatment outcomes in cocaine addiction, where pre-treatment connectivity within and between the frontoparietal, salience, and reward networks forecasted abstinence rates and generalized across independent cohorts.[226] Notably, neural predictors show substance specificity: networks predicting cocaine abstinence did not generalize to cannabis, for which a distinct abstinence network was identified.[227] Other biomarkers add further precision—for instance, an oscillatory EEG signature linked to melanin-concentrating hormone neuron activity predicted cocaine-seeking behavior in preclinical models. Finally, impairments in waiting impulsivity, associated with hypoconnectivity between the subthalamic nucleus, ventral striatum, and subgenual cingulate, have been linked transdiagnostically to alcohol misuse, highlighting cortico-striatal-thalamic circuits as promising targets for neuromodulation.[228]

Therapy for mental disorders using BCI

Open-loop approaches have been widely implemented across psychiatric disorders, most notably through repetitive TMS and tDCS. In MDD, fixed-parameter TMS targeting the left dorsolateral prefrontal cortex and bifrontal tDCS protocols are standard open-loop strategies, with multiple randomized and open-label trials reporting significant symptom reduction.[229,230] In BD, open-label and home-based tDCS interventions have shown feasibility and clinical benefit, particularly in bipolar depression, with good tolerability and improvements in mood symptoms.[231]

In schizophrenia, TMS has been tested as an adjunctive treatment for negative and cognitive symptoms. For example, deep-TMS delivered with fixed high-frequency protocols demonstrated significant improvements in negative symptom scales compared with sham stimulation.[232] Systematic reviews and meta-analyses further support moderate benefits of TMS on negative symptoms, though heterogeneity remains high.[233,234]

In SUD, both TMS[235] and tDCS have been applied in open-loop paradigms to reduce craving. Robust evidence indicates that both TMS[236–239] and tDCS[240,241] are effective in reducing craving in patients with alcohol, cocaine, and nicotine use disorders.[242,243]

Collectively, these open-loop neuromodulation strategies are safe, relatively simple to administer, and clinically accessible, providing meaningful symptom relief across a range of psychiatric conditions. However, by delivering stimulation with fixed parameters independent of real-time neural states, they remain limited in their ability to accommodate individual heterogeneity or dynamically optimize treatment response.

The closed-loop mode represents the core advantage of BCI technology, with its key feature being the establishment of a complete read–compute–write loop. In this mode, the system can acquire neural signals from the patient in real time, analyze them using algorithms to identify brain activity patterns associated with pathological states, and accordingly adjust the timing and parameters of stimulation, thereby achieving individualized and precise interventions.

In the treatment of psychiatric disorders, adaptive DBS represents a typical example of closed-loop intervention.[244] Electrodes are implanted in regions such as the anterior cingulate cortex or nucleus accumbens to continuously monitor local field potential signals associated with depressive[245] or obsessive–compulsive symptoms,[246] with stimulation delivered only when abnormal activity is detected, thereby avoiding ineffective or excessive intervention. Another direction is EEG-based closed-loop regulation, where systems monitor emotion-related electrophysiological markers such as alpha or theta oscillations in real time and automatically adjust the parameters of TMS or tDCS to achieve treatments more closely aligned with an individual's brain state.[247–249] More recently, temporal interference (TI) stimulation,[250] an emerging non-invasive technique, has been proposed for closed-loop use. By generating interfering electric fields to selectively target deep brain structures, TI stimulation offers the potential for individualized and precise interventions in conditions such as schizophrenia,[251] MDD[252] and BD[253] when integrated with real-time neural or behavioral markers.

The advantages of such closed-loop approaches include a higher degree of individualization, reduced unnecessary stimulation and side effects, and greater compatibility with the dynamic and fluctuating nature of psychiatric symptoms. However, their clinical application remains limited by the difficulty of reliable signal interpretation, device complexity, and insufficient clinical validation.

Challenges of BCI in mental disorders

Despite the considerable promise of BCI technology in mental disorders, several conceptual and practical challenges remain. A core issue is the inherent complexity and variability of neural signals associated with psychiatric conditions. Unlike motor commands, which can be relatively well-localized and consistent, cognitive and affective states such as craving, sadness, or hallucinations are distributed, dynamic, and highly idiosyncratic. This makes it difficult to identify reliable, generalizable neural biomarkers that can be decoded accurately across a diverse patient population. Moreover, the noisy, non-stationary nature of EEG or other neurophysiological data in real-world settings—where patients may be anxious, distracted, or medicated—adds another layer of difficulty for developing robust BCI systems that perform

Table 3. A roadmap for clinical translation of BCI for neurological disorders.

Phase & Timeline	Key Goals and Milestones
Phase 1: Near-Term Foundations (Next 5 Years)	• **Hardware Stability:** Develop and validate next-generation, biocompatible electrodes (e.g., flexible, bioresorbable) for long-term signal stability • **Biomarker Validation:** Establish robust, standardized neural biomarkers for diagnosis and closed-loop control through large-scale multi-center studies • **Real-World Efficacy:** Demonstrate functional improvement in activities of daily living (ADLs) in home and community settings
Phase 2: Mid-Term Integration (5-10 Years)	• **Adaptive Closed-Loop Systems:** Achieve AI-driven, real-time neuromodulation that dynamically adjusts to sensed neural states • **Multimodal Data Fusion:** Integrate EEG with fNIRS, fMRI, and other signals to create a comprehensive picture of brain function for enhanced accuracy • **Clinical Translation:** Develop standardized, "plug-and-play" BCI platforms with automated calibration to increase accessibility and reduce expert dependency
Phase 3: Long-Term Transformation (10+ Years)	• **Holistic Restoration:** Create integrated systems for simultaneous sensory, motor, and cognitive restoration, moving beyond single-modality treatment • **Proactive Neurohealth:** Evolve BCIs from therapeutic tools to systems for continuous brain monitoring and predictive health management • **Ethical & Regulatory Frameworks:** Establish comprehensive guidelines for long-term data privacy, identity, and equitable access

consistently outside controlled lab environments.

Translating experimental BCI protocols into clinically viable tools also faces significant hurdles. Many current approaches rely on expensive, immobile equipment like high-density EEG or fMRI setups, which are impractical for widespread clinical deployment or continuous monitoring in daily life. There's a tension between the desire for high-resolution neural data and the need for affordable, wearable, user-friendly devices. Furthermore, the closed-loop modulation of brain activity—especially using neurofeedback or real-time neuromodulation—raises unique ethical and clinical questions in psychiatry. For instance, could continuously decoding a patient's emotional state invade their autonomy or privacy? What happens if a system misinterprets neural activity and delivers inappropriate stimulation? These concerns are particularly acute when dealing with vulnerable individuals whose capacity for informed consent may be compromised by their illness.

Finally, the ultimate challenge may lie not in the technology itself, but in integrating it meaningfully into psychiatric care. BCIs are unlikely to offer standalone cures; rather, they must be part of a broader therapeutic strategy that includes psychotherapy, pharmacotherapy, and social support. Clinicians will need training to interpret BCI-derived data and incorporate it into individualized treatment plans. Moreover, the field must avoid over-reducing complex human experiences to neural patterns—acknowledging that a biomarker of "anhedonia" is not the same as understanding the personal reality of living without pleasure. Success will depend on developing BCIs that enhance rather than replace the therapeutic relationship, providing tools that empower both patients and clinicians in the shared pursuit of recovery.

A ROADMAP FOR BCI CLINICAL TRANSLATION

The transformative potential of BCI for neurological disorders hinges on systematically addressing key challenges. By synthesizing the insights from this review, we propose a three-phase roadmap that transitions from solving foundational challenges to achieving disruptive, holistic neurotherapeutics (Table 3). In the near-term (next 5 years), the focus must be on establishing clinical viability. This involves developing next-generation, biocompatible electrodes for long-term stability, validating robust neural biomarkers for each disorder through large-scale studies, and demonstrating real-world efficacy of BCI systems in improving patients' activities of daily living. Success in this phase is the critical foundation for all future applications.

The mid-term (5-10 years) will be characterized by integration and personalization. With reliable hardware and biomarkers, the field will shift towards creating adaptive, closed-loop systems where AI algorithms modulate neural stimulation in real-time based on sensed brain activity. A key milestone will be the seamless fusion of multimodal data (e.g., EEG, fNIRS) to enhance decoding accuracy for complex states. Furthermore, efforts will focus on standardizing platforms to create more accessible "plug-and-play" BCI technologies, moving them from specialized labs to broader clinical settings.

The long-term vision (10+ years) points towards disruptive innovation and a paradigm shift in neurohealth. The culmination of prior advances will enable fully integrated systems that provide simultaneous sensory, motor, and cognitive restoration, moving beyond treating single deficits. BCIs will evolve from reactive therapies to proactive tools for continuous brain health monitoring, capable of predicting and preventing disease exacerbations. Ultimately, this progress must be accompanied by the establishment of comprehensive ethical and regulatory frameworks to ensure the responsible and equitable integration of BCIs into society.

CONCLUSION

BCI technology demonstrates remarkable potential in bridging neural activity with external systems, opening up entirely new avenues for the diagnosis and treatment of brain disorders. Ranging from helping patients restore sensory and motor functions to enhancing cognitive abilities and intervening in mental illnesses, BCI is steadily breaking through the experimental limitations of the proof-of-concept phase and gradually advancing toward the practical level with clinical application value. This multidisciplinary technological advancement not only highlights the practical value of BCI as an auxiliary tool but also establishes its core position as an innovative diagnostic and therapeutic platform, injecting profound influence into promoting the development of precision medicine and reshaping the diagnostic and therapeutic paradigm for brain disorders.

However, the field still faces numerous significant challenges. Current BCI technology has notable limitations in core performance: first, the decoding accuracy of neural signals has not yet reached the ideal standard for clinical applications, making it difficult to accurately capture complex brain activity commands. This gap between ideal and actual performance is particularly evident when contrasted with the target benchmarks required for reliable clinical utility across different disorders. For instance, while high-grade motor control for complex activities of daily living may require decoding accuracies exceeding 95%, current systems for motor disorders often achieve levels between 70-85% in controlled environments. Similarly, for cognitive disorders, accurately distinguishing between subtle subtypes like Alzheimer's disease and frontotemporal dementia using EEG-based biomarkers may demand accuracies above 90%, yet many existing frameworks operate near 80-85%. In sensory restoration, such as providing functional artificial vision, meaningful phosphene mapping might necessitate near-perfect spatial decoding, a target far beyond the current capabilities of even the most advanced cortical implants. Second, in dynamic daily scenarios, the system lacks robustness, being vulnerable to factors such as movement and environmental interference, and its stability urgently needs improvement; third, the issue of long-term biocompatibility of implantable devices has not been fully addressed,

which may trigger inflammatory reactions or tissue rejection, restricting the safety of their long-term use. At the same time, the complex pathological mechanisms of brain disorder themselves, combined with the physiological and pathological heterogeneity among individual patients, further increase the difficulty in developing universal clinical solutions, making it hard for the technology to quickly adapt to the practical needs of different cases.

Furthermore, considerations regarding ethics and regulation cannot be ignored either. From the protection of privacy information carried by patients' electroencephalographic signals, to the standards for adequate informed consent in invasive procedures, and to the risk of cognitive manipulation that may arise from the potential abuse of the technology. All these issues require the establishment of clear industry guidelines and regulatory frameworks before BCI technology is widely implemented, so as to ensure that technological development is always aligned with ethical boundaries and social security.

In the future, the next generation of BCIs will integrate multimodal neural signals, advanced machine learning algorithms, and closed-loop adaptive modulation technology more deeply, thereby achieving more reliable operational performance and more precise personalized interventions. Of particular importance is the deep integration of BCIs with artificial intelligence, neuroimaging, and neuromodulation technology, it is expected to fundamentally improve the diagnostic accuracy of brain disorders while optimizing the effectiveness of treatment plans, providing brand-new technical support for the diagnosis and treatment of complex brain conditions. Furthermore, the advancement of large-scale clinical trials, the conduct of long-term follow-up studies, and interdisciplinary collaboration across fields such as engineering, medicine, and neuroscience are even more essential core guarantees for transforming BCI from a laboratory technology into a safe, effective, and accessible healthcare solution; none of these elements can be dispensed with.

In summary, although the BCI field still faces numerous challenges that need to be overcome, the continuous iteration and innovation of its technology have injected tremendous hope into breaking the limitations of brain disorder diagnosis and treatment and reshaping the prospects of clinical practice. With the deepening of technological innovation and the responsible implementation that balances ethics and safety, BCIs will surely become an indispensable and crucial component of future neurotherapeutic strategies, bringing new opportunities for recovery to brain disorder patients around the world.

REFERENCES

1. Wang Z., Wang S.-N., Xu T.-Y., et al. (2017). Organoid technology for brain and therapeutics research. *CNS Neurosci. Ther.* **23**:771–778. DOI:10.1111/cns.12754
2. Issack P.S, Cunningham M.E, Pumberger M, et al. (2012). Degenerative lumbar spinal stenosis: Evaluation and management. *JAAOS* **20**:527–535. DOI:10.5435/JAAOS-20-08-527
3. Cruz M.V., Jamal S. and Sethuraman S.C. (2025). A comprehensive survey of brain-computer interface technology in health care: Research perspectives. *J. Med. Signals Sens.* **15**:6–16. DOI:10.4103/jmss.jmss_49_24
4. Mohanty R., Sinha A.M., Remsik A.B., et al. (2018). Machine learning classification to identify the stage of brain-computer interface therapy for stroke rehabilitation using functional connectivity. *Front. Neurosci.* **12**:353. DOI:10.3389/fnins.2018.00353
5. Ma J., Wang Y., Yang J., et al. (2024). In vivo bioelectronic nose based on a bioengineered rat for the explosive odors with Benzene ring detection and identification. *ICBBE* **24**:110–114. DOI:10.1145/3707127.3707145
6. Sun G., Liu Z., Gan L., et al. (2025). SpikeNAS-bench: Benchmarking NAS algorithms for spiking neural network architecture. *IEEE Trans Artif Intell* **6**:1614–1625. DOI:10.1109/tai.2025.3534136
7. Cao L., Zhao W. and Sun B. (2025). Emotion recognition using multi-scale EEG features through graph convolutional attention network. *Neural Netw.* **184**:107060. DOI:10.1016/j.neunet.2024.107060
8. Liu X., Lu Z., Li J., et al. (2024). An 8-channel high-voltage neural stimulation IC design with exponential waveform output. *Neuroelectronics.* **1**:0001. DOI:10.55092/neuroelectronics20240001
9. Ramadan R.A. and Altamimi A.B. (2024). Unraveling the potential of brain-computer interface technology in medical diagnostics and rehabilitation: A comprehensive literature review. *Health Technol.* **14**:263–276. DOI:10.1007/s12553-024-00822-1
10. Bashashati A, Fatourechi M, Ward R.K, et al. (2007). A survey of signal processing algorithms in brain–computer interfaces based on electrical brain signals. *J. Neural Eng.* **4**:R32. DOI:10.1088/1741-2560/4/2/R03
11. Edelman B.J., Zhang S., Schalk G., et al. (2025). Non-invasive brain-computer interfaces: State of the art and trends. *IEEE Rev. Biomed. Eng.* **18**:26–49. DOI:10.1109/RBME.2024.3449790
12. Wen D., Fan Y., Hsu S.-H., et al. (2021). Combining brain-computer interface and virtual reality for rehabilitation in neurological diseases: A narrative review. *Ann Phys Rehabil Med* **64**:101404. DOI:10.1016/j.rehab.2020.03.015
13. Zhang H., Jiao L., Yang S., et al. (2024). Brain-computer interfaces: The innovative key to unlocking neurological conditions. *Int JSurg* **110**:5745–5762. DOI:10.1097/js9.0000000000002022
14. Fatourechi M., Bashashati A., Ward R.K., et al. (2007). EMG and EOG artifacts in brain computer interface systems: A survey. *Neurophysiol Clin* **118**:480–494. DOI:10.1016/j.clinph.2006.10.019
15. Sun B., Lv J.-J., Rui L.-G., et al. (2021). Seizure prediction in scalp EEG based channel attention dual-input convolutional neural network. *PhyA* **584**:126376. DOI:10.1016/j.physa.2021.126376
16. Sun B., Zhang H., Wu Z., et al. (2021). Adaptive spatiotemporal graph convolutional networks for motor imagery classification. *IEEE Signal Process. Lett.* **28**:219–223. DOI:10.1109/lsp.2021.3049683
17. Sun B., Zhao X., Zhang H., et al. (2021). EEG motor imagery classification with sparse spectrotemporal decomposition and deep learning. *IEEE Trans. Autom. Sci. Eng.* **18**:541–551. DOI:10.1109/tase.2020.3021456
18. Sironi V.A. (2011). Origin and evolution of deep brain stimulation. *Front. Integr. Neurosci.* **5**:42–42. DOI:10.3389/fnint.2011.00042
19. Mane R., Chouhan T. and Guan C. (2020). BCI for stroke rehabilitation: Motor and beyond. *J. Neural Eng.* **17**:041001. DOI:10.1088/1741-2552/aba162
20. Hochberg L.R. and Donoghue J.P. (2006). Sensors for brain-computer interfaces - Options for turning thought into action. *IEEE Eng. Med. Biol. Mag.* **25**:32–38. DOI:10.1109/memb.2006.1705745
21. Cohen M.X. (2017). Where does EEG come from and what does it mean. *Trends Neurosci.* **40**:208–218. DOI:10.1016/j.tins.2017.02.004
22. Zhang H, Zhou Q.Q, Chen H, et al. (2023). The applied principles of EEG analysis methods in neuroscience and clinical neurology. *MILITARY MED. RES.* **10**:67. DOI:10.1186/s40779-023-00502-7
23. Liu Z., Hao X., Wu T., et al. (2023). A bimodal registration and attention method for speed imagery brain-computer interface. *BAC* **2**:1. DOI:10.1080/27706710.2023.2285052
24. Trentini C., Pagani M., Fania P., et al. (2015). Neural processing of emotions in traumatized children treated with Eye Movement Desensitization and Reprocessing therapy: A hdEEG study. *Front. Psychol.* **6**:1662. DOI:10.3389/fpsyg.2015.01662
25. Cheyne D.O. (2013). MEG studies of sensorimotor rhythms: A review. *Exp. Neurol.* **245**:27–39. DOI:10.1016/j.expneurol.2012.08.030
26. Logothetis N. K. (2008). What we can do and what we cannot do with fMRI. *Nature* **453**:869–878. DOI:10.1038/nature06976
27. Smith S.M. (2004). Overview of fMRI analysis. *Br. J. Radiol.* **77**:S167–S175. DOI:10.1259/bjr/33553595
28. Van de Ville D., Blu T. and Unser M. (2006). Surfing the brain - An overview of wavelet-based techniques for fMRI data analysis. *IEEE Eng. Med. Biol. Mag.* **25**:65–78. DOI:10.1109/memb.2006.1607671
29. Worsley K.J. (1997). An overview and some new developments in the statistical analysis of PET and fMRI data. *Hum. Brain Mapp.* **5**:254–258. DOI:10.1002/(SICI)1097-0193(1997)5:4%3C254::AID-HBM9%3E3.0.CO;2-2
30. Tak S. and Ye J.C. (2014). Statistical analysis of fNIRS data: A comprehensive review. *Neuroimage* **85**:72–91. DOI:10.1016/j.neuroimage.2013.06.016
31. Tian J., Wang J., Quan W., et al. (2019). The functional near-infrared spectroscopy in the diagnosis of schizophrenia. *Eur J Psychiatry* **33**:97–103. DOI:10.1016/j.ejpsy.2019.05.001
32. Sirpal P., Kassab A., Pouliot P., et al. (2019). fNIRS improves seizure detection in multimodal EEG-fNIRS recordings. *J. Biomed. Opt.* **24**:051408. DOI:10.1117/1.Jbo.24.5.051408
33. Sun B., Liu Z., Wu Z., et al. (2023). Graph convolution neural network based end-to-end channel selection and classification for motor imagery brain–computer interfaces. *IEEE Trans. Ind. Inform.* **19**:9314–9324. DOI:10.1109/tii.2022.3227736
34. Walter U., Behnke S., Eyding J., et al. (2007). Transcranial brain parenchyma sonography in movement disorders: State of the art. *Ultrasound Med. Biol.* **33**:15–25. DOI:10.1016/j.ultrasmedbio.2006.07.021
35. Berg D., Godau J. and Walter U. (2008). Transcranial sonography in movement disorders. *Lancet Neurol.* **7**:1044–1055. DOI:10.1016/s1474-4422(08)70239-4
36. Sanzaro E. and Iemolo F. (2016). Transcranial sonography in movement disorders: an interesting tool for diagnostic perspectives. *Neurol. Sci.* **37**:373–376. DOI:10.1007/s10072-015-2424-6
37. Oribe S., Yoshida S., Kusama S., et al. (2019). Hydrogel-based organic subduralelectrode with high conformability to brain surface. *Sci. Rep.* **9**:13379. DOI:10.1038/s41598-019-49772-z
38. Janjarasjitt S. and Loparo K.A. (2014). Scale-Invariant behavior of epileptic ECoG. *J. Med. Biol. Eng.* **34**:535–541. DOI:10.5405/jmbe.1433
39. Branco M.P., Geukes S.H., Aarnoutse E.J., et al. (2023). Nine decades of electrocorticography: A comparison between epidural and subdural recordings. *Eur. J. Neurosci.* **57**:1260–1288. DOI:10.1111/ejn.15941
40. Guenot M., Isnard J., Ryvlin P., et al. (2001). Neurophysiological monitoring for

epilepsy surgery: The talairach SEEG method. *Stereotact. Funct. Neurosurg.* **77**:29–32. DOI:10.1159/000064595
41. Buzsáki G. (2004). Large-scale recording of neuronal ensembles. *Nat. Neurosci.* **7**:446–451. DOI:10.1038/nn1233
42. Chen T.W., Wardill T.J., Sun Y., et al. (2013). Ultrasensitive fluorescent proteins for imaging neuronal activity. *Nature* **499**:295–300. DOI:10.1038/nature12354
43. Grienberger C., Giovannucci A., Zeiger W., et al. (2022). Two-photon calcium imaging of neuronal activity. *Nat. Rev. Method. Prim.* **2**:67. DOI:10.1038/s43586-022-00147-1
44. Ren C. and Komiyama T. (2021). Characterizing cortex-wide dynamics with wide-field calcium imaging. *J. Neurosci.* **41**:4160–4168. DOI:10.1523/JNEUROSCI.3003-20.2021
45. Chen K., Tian Z. and Kong L. (2022). Advances of optical miniscopes for in vivo imaging of neural activity in freely moving animals. *Front. Neurosci.* **16**:994079. DOI:10.3389/fnins.2022.994079
46. Packer A.M., Russell L.E., Dalgleish H.W.P., et al. (2015). Simultaneous all-optical manipulation and recording of neural circuit activity with cellular resolution in vivo. *Nat. Methods* **12**:140–146. DOI:10.1038/nmeth.3217
47. Maiseli B., Abdalla A.T., Massawe L.V., et al. (2023). Brain-computer interface: Trend, challenges, and threats. *Brain Inform* **10**:20. DOI:10.1186/s40708-023-00199-3
48. Wu Z., Sun B. and Zhu X. (2022). Coupling convolution, transformer and graph embedding for motor imagery brain-computer interfaces. *ISCAS* **2024**:404–408. DOI:10.1109/ISCAS48785.2022.9937435
49. Reed T. and Cohen Kadosh R. (2018). Transcranial electrical stimulation (tES) mechanisms and its effects on cortical excitability and connectivity. *J Inherit Metab Dis* **41**:1123–1130. DOI:10.1007/s10545-018-0181-4
50. Yu Y., Wang H., Liu X., et al. (2024). Closed-loop transcranial electrical stimulation for inhibiting epileptic activity propagation: A whole-brain model study. *Nonlinear Dyn.* **112**:21369–21387. DOI:10.1007/s11071-024-10132-w
51. Afsharian F., Abadi R.K., Taheri R., et al. (2024). Transcranial direct current stimulation combined with cognitive training improves two executive functions: Cognitive flexibility and information updating after traumatic brain injury. *Acta Psychol* **250**:104553. DOI:10.1016/j.actpsy.2024.104553
52. Brunoni A.R., Amadera J., Berbel B., et al. (2012). A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. *Int. J. Neuropsychopharmacol.* **16**:445–456. DOI:10.1017/S1461145712000490
53. Legon W., Sato T.F., Opitz A., et al. (2014). Transcranial focused ultrasound modulates the activity of primary somatosensory cortex in humans. *Nat. Neurosci.* **17**:322–329. DOI:10.1038/nn.3620
54. Folloni D., Verhagen L., Mars R.B., et al. (2019). Manipulation of subcortical and deep cortical activity in the primate brain using transcranial focused ultrasound stimulation. *Neuron* **101**:1109–1116.e5. DOI:10.1101/342303
55. Blackmore J., Shrivastava S., Sallet J., et al. (2019). Ultrasound neuromodulation: A review of results, mechanisms and safety. *Ultrasound Med. Biol.* **45**:1509–1536. DOI:10.1016/j.ultrasmedbio.2018.12.015
56. Hett D., Rogers J., Humpston C., et al. (2021). Repetitive transcranial magnetic stimulation (rTMS) for the treatment of depression in adolescence: A systematic review. *J Affect Disord* **278**:460–469. DOI:10.1016/j.jad.2020.09.058
57. Zhou D., Li X., Wei S., et al. (2024). Transcranial direct current stimulation combined with repetitive transcranial magnetic stimulation for depression: A randomized clinical trial. *JAMA Netw Open.* **7**:e2444306. DOI:10.1001/jamanetworkopen.2024.44306
58. Kobayashi M. and Pascual-Leone A. (2003). Transcranial magnetic stimulation in neurology. *Lancet Neurol.* **2**:145–156. DOI:10.1016/s1474-4422(03)00321-1
59. Zhong G., Yang Z. and Jiang T. (2021). Precise modulation strategies for transcranial magnetic stimulation: Advances and future directions. *Neurosci. Bull.* **37**:1718–1734. DOI:10.1007/s12264-021-00781-x
60. Sorkhabi M.M., Benjaber M., Wendt K., et al. (2021). Programmable transcranial magnetic stimulation: A modulation approach for the generation of controllable magnetic stimuli. *IEEE Trans. Biomed. Eng.* **68**:1847–1858. DOI:10.1109/TBME.2020.3024902
61. Hariz M. (2014). Deep brain stimulation: New techniques. *Parkinsonism Relat. Disord.* **1**:S192–196. DOI:10.1016/S1353-8020(13)70045-2
62. Hariz M. and Blomstedt P. (2022). Deep brain stimulation for Parkinson's disease. *J Intern Med* **292**:764–778. DOI:10.1111/joim.13541
63. Fox M.D. and Alterman R.L. (2015). Brain stimulation for Torsion Dystonia. *JAMA Neurol.* **72**:713–719. DOI:10.1001/jamaneurol.2015.51
64. Sarica C., Iorio-Morin C., Aguirre-Padilla D.H., et al. (2021). Implantable pulse generators for deep brain stimulation: Challenges, complications, and strategies for practicality and longevity. *Front. Hum. Neurosci.* **15**:708481. DOI:10.3389/fnhum.2021.708481
65. Espinoza R.T., and Kellner C.H. (2022). Electroconvulsive therapy. *N. Engl. J. Med.* **386**:667–672. DOI:10.1056/NEJMra2034954
66. DiMarco A.F., Kowalski K.E., Geertman R.T., et al. (2006). Spinal cord stimulation: A new method to produce an effective cough in patients with spinal cord injury. *Am J Respir Crit Care Med.* **173**:1386–1389. DOI:10.1164/rccm.200601-097CR
67. Gerasimenko Y., Gorodnichev R., Puhov A., et al. (2015). Initiation and modulation of locomotor circuitry output with multisite transcutaneous electrical stimulation of the spinal cord in noninjured humans. *J. Neurophysiol.* **113**:834–842. DOI:10.1152/jn.00609.2014
68. Ahmadi R., Hajiabadi M.M., Unterberg A., et al. (2021). Wireless spinal cord stimulation technology for the treatment of neuropathic pain: A single-center experience. *Neuromodulation* **24**:591–595. DOI:10.1111/ner.13149
69. Dorrian R.M., Berryman C.F., Lauto A., et al. (2023). Electrical stimulation for the treatment of spinal cord injuries: A review of the cellular and molecular mechanisms that drive functional improvements. *Front. Cell. Neurosci.* **17**:1095259. DOI:10.3389/fncel.2023.1095259
70. Sun B., Feng H., Chen K., et al. (2016). A deep learning framework of quantized compressed sensing for wireless neural recording. *IEEE Access* **4**:5169–5178. DOI:10.1109/access.2016.2604397
71. Deisseroth K. (2015). Optogenetics: 10 years of microbial opsins in neuroscience. *Nat. Neurosci.* **18**:1213–1225. DOI:10.1038/nn.4091
72. Sahel J.A., Boulanger-Scemama E., Pagot C., et al. (2021). Partial recovery of visual function in a blind patient after optogenetic therapy. *Nat. Med.* **27**:1223–1229. DOI:10.1038/s41591-021-01351-4
73. Brandt T., Dieterich M. and Huppert D. (2024). Human senses and sensors from Aristotle to the present. *Front. Neurol.* **15**:1404720. DOI:10.3389/fneur.2024.1404720
74. Ozieblo D., Leja M.L., Skarzynski H., et al. (2020). Wide spectrum of genetic hearing loss causes and large number of novel variants in cochlea implanted children. *Eur. J. Hum. Genet.* **28**:190–190.
75. Genovese F., Romeo M., Terrenzio F.P., et al. (2025). Distinct patterns of visuo-tactile and visuo-motor body-related integration in Parkinson's disease. *Sci. Rep.* **15**:27923. DOI:10.1038/s41598-025-08965-5
76. Hohmann V. (2023). The future of hearing aid technology Can technology turn us into superheroes. *Z. Gerontol. Geriatr.* **56**:283–289. DOI:10.1007/s00391-023-02179-y
77. Motiwala A., Soldado-Magraner J., Batista A.P., et al. (2025). Brain-computer interfaces as a causal probe for scientific inquiry. *Trends Cogn. Sci.* **30**:40-53. DOI:10.1016/j.tics.2025.06.017
78. Dohle E., Swanson E., Jovanovic L., et al. (2025). Toward the clinical translation of implantable brain-computer interfaces for motor impairment: Research trends and outcome measures. *Adv. Sci.* **12**:e01912. DOI:10.1002/advs.202501912
79. Oshitari T. (2024). Translational research and therapies for neuroprotection and regeneration of the optic nerve and retina: A narrative review. *Int. J. Mol. Sci.* **25**:10485. DOI:10.3390/ijms251910485
80. Wang G., Marcucci G., Peters B., et al. (2024). Human-centred physical neuromorphics with visual brain-computer interfaces. *Nat. Commun.* **15**:6393. DOI:10.1038/s41467-024-50775-2
81. Waytowich N.R. and Krusienski D.J. (2015). Spatial decoupling of targets and flashing stimuli for visual brain-computer interfaces. *J. Neural Eng.* **12**:036006. DOI:10.1088/1741-2560/12/3/036006
82. Hao X. and Sun B. (2022). Speed imagery EEG classification with spatial-temporal feature attention deep neural networks . *ISCAS* **2022**:9937802. DOI:10.1109/iscas48785.2022.9937802
83. Van Hoof R., Lozano A., Wang F., et al. (2025). Optimal placement of high-channel visual prostheses in human retinotopic visual cortex. *J. Neural Eng.* **22**:026016. DOI:10.1088/1741-2552/adaeef
84. Fernández E., Alfaro A., Soto-Sánchez C., et al. (2021) .Visual percepts evoked with an intracortical 96-channel microelectrode array inserted in human occipital cortex. *JCI* **131**:3002896. DOI:10.1371/journal.pbio.3002896
85. Shams L., Kamitani Y., Thompson S., et al. Sound alters visual evoked potentials in humans. *Neuroreport* **12**:3849-3852. DOI:10.1097/00001756-200112040-00049
86. Ni G., Zheng Q., Liu Y., et al. (2021). Objective electroencephalography-based assessment for auditory rehabilitation of pediatric cochlear implant users. *Hear. Res.* **404**:108211. DOI:10.1016/j.heares.2021.108211
87. Lefebvre P.P., Mueller J., Mark G., et al. (2025). Rehabilitation of human hearing with a totally implantable cochlear implant: a feasibility study. *Commun. Med.* **5**:10. DOI:10.1038/s43856-024-00719-0
88. Zheng Q., Wu Y., Zhu J., et al. (2025). Applications and challenges of auditory brain-computer interfaces in objective auditory assessments for pediatric cochlear implants. *Exploration* **5**:20240078. DOI:10.1002/exp.20240078
89. Deroche M.L.D., Wolfe J., Neumann S., et al. (2023). Auditory evoked response to an oddball paradigm in children wearing cochlear implants. *Clin. Neurophysiol.* **149**:133–145. DOI:10.1016/j.clinph.2023.02.179
90. Lee H.-J., Smieja D., Polonenko M.J., et al. (2020). Consistent and chronic cochlear implant use partially reverses cortical effects of single sided deafness in children. *Sci. Rep.* **10**:21526. DOI:10.1038/s41598-020-78371-6
91. Hong Y., Ryun S. and Chung C.K. (2024). Evoking artificial speech perception through invasive brain stimulation for brain-computer interfaces: Current challenges and future perspectives. *Front. Neurosci.* **18**:1428256. DOI:10.3389/fnins.2024.1428256
92. Abrams Z. (2023). Breakthroughs in Brain Implants. *IEEE Pulse* **14**:7–10. DOI:10.1109/mpuls.2024.3353668
93. Miklos G., Halasz L., Hasslberger M., et al. (2024). Sensory-substitution based sound perception using a spinal computer-brain interface. *Sci. Rep.* **14**:24879. DOI:10.1038/s41598-024-75779-2

94. Moehring F., Halder P., Seal R.P., et al. (2018). Uncovering the cells and circuits of touch in normal and pathological settings. *Neuron* **100**:349–360. DOI:10.1016/j.neuron.2018.10.019
95. Flesher S.N., Downey J.E., Weiss J.M., et al. (2021). A brain-computer interface that evokes tactile sensations improves robotic arm control. *Science* **372**:831–836. DOI:10.1126/science.abd0380
96. Oknina L., Strelnikova E., Lin L.F., et al. (2025). Alterations in functional connectivity of the brain during postural balance maintenance with auditory stimuli: A stabilometry and electroencephalogram study. *Biomed. Phys. Eng. Express* **11**:035006. DOI:10.1088/2057-1976/adbf26
97. Xu T., Clemson L., O'Loughlin K., et al. (2018). Risk factors for falls in community stroke survivors: A systematic review and meta-analysis. *Arch. Phys. Med. Rehabil.* **99**:563–573. DOI:10.1016/j.apmr.2017.06.032
98. Marín-Medina D.S., Arenas-Vargas P.A., Arias-Botero J.C., et al. (2024). New approaches to recovery after stroke. *Neurol. Sci.* **45**:55–63. DOI:10.1007/s10072-023-07012-3
99. Sun B., Song B., Lv J., et al. (2023). A multiscale feature extraction network based on channel-spatial attention for electromyographic signal classification. *IEEE Trans. Cogn. Dev. Syst.* **15**:591–601. DOI:10.1109/tcds.2022.3167042
100. Yang Q., Zhou G., Noto T., et al. (2022). Smell-induced gamma oscillations in human olfactory cortex are required for accurate perception of odor identity. *PLoS. Biol.* **20**:e3001509. DOI:10.1371/journal.pbio.3001509
101. Kasprzak H., Niewinska N., Komendzinski T., et al. (2024). Improving the classification of olfactory brain-computer interface responses by combining EEG and EBG signals. *EMBC* **2024**:1–4. DOI:10.1109/embc53108.2024.10782826
102. Ninenko I., Kleeva D.F., Bukreev N., et al. (2023). An experimental paradigm for studying EEG correlates of olfactory discrimination. *Front. Hum. Neurosci.* **17**:1117801. DOI:10.3389/fnhum.2023.1117801
103. Oleszkiewicz A., Croy I. and Hummel T. (2025). The impact of olfactory loss on quality of life: A 2025 review. *Chem. Senses* **50**:bjaf023. DOI:10.1093/chemse/bjaf023
104. Sakai M., Kazui H., Shigenobu K., et al. (2017). Gustatory dysfunction as an early symptom of semantic dementia. *Dement. Geriatr. Cogn. Disord. Extra* **7**:395–405. DOI:10.1159/000481854
105. Wang X., Bai G., Liang J., et al. (2024). Gustatory interface for operative assessment and taste decoding in patients with tongue cancer. *Nat. Commun.* **15**:8967. DOI:10.1038/s41467-024-53379-y
106. Sun B., Wu Z., Hu Y., et al. (2022). Golden subject is everyone: A subject transfer neural network for motor imagery-based brain computer interfaces. *Neural Netw.* **151**:111–120. DOI:10.1016/j.neunet.2022.03.025
107. Merritt H.H. (1978). Brain's diseases of the nervous system. *Am. J. Psychiat.* **135**:259–259. DOI:10.1176/ajp.135.2.259
108. Roth R.H. and Ding J.B. (2024). Cortico-basal ganglia plasticity in motor learning. *Neuron* **112**:2486–2502. DOI:10.1016/j.neuron.2024.06.014
109. Obeso J.A., Stamelou M., Goetz C.G., et al. (2017). Past, present, and future of Parkinson's disease: A special essay on the 200th anniversary of the shaking palsy. *J. Mov. Disord.* **32**:1264–1310. DOI:10.1002/mds.27115
110. Hardiman O., Al-Chalabi A., Chio A., et al. (2017). Amyotrophic lateral sclerosis. *Nat Rev Dis Primers* **3**:17071. DOI:10.1038/nrdp.2017.71
111. Hankey G.J. (2017). Stroke. *Lancet* **389**:641–654. DOI:10.1016/s0140-6736(16)30962-x
112. Lammertse D., Tuszynski M.H., Steeves J.D., et al. (2007). Guidelines for the conduct of clinical trials for spinal cord injury as developed by the ICCP panel: Clinical trial design. *Spinal Cord* **45**:232–242. DOI:10.1038/sj.sc.3102010
113. Filip P., Lungu O.V., Manto M.U., et al. (2016). Linking essential tremor to the cerebellum: physiological evidence. *Cerebellum* **15**:774–780. DOI:10.1007/s12311-015-0740-2
114. Grefkes C. and Fink G.R. (2020). Recovery from stroke: current concepts and future perspectives. *Neurol. Res. Pract.* **2**:17. DOI:10.1186/s42466-020-00060-6
115. Hammond C., Bergman H. and Brown P. (2007). Pathological synchronization in Parkinson's disease: Networks, models and treatments. *Trends Neurosci* **30**:357–364. DOI:10.1016/j.tins.2007.05.004
116. Pfurtscheller G. and Lopes da Silva F.H. (1999). Event-related EEG/MEG synchronization and desynchronization: Basic principles. *Clin Neurophysiol* **110**:1842–1857. DOI:10.1016/s1388-2457(99)00141-8
117. Nasseroleslami B., Dukic S., Broderick M., et al. (2019). Characteristic increases in EEG connectivity correlate with changes of structural MRI in amyotrophic lateral sclerosis. *Cereb Cortex* **29**:27–41. DOI:10.1093/cercor/bhx301
118. Herff C., Heger D., Fortmann O., et al. (2013). Mental workload during n-back task-quantified in the prefrontal cortex using fNIRS. *Front Hum Neurosci* **7**:935. DOI:10.3389/fnhum.2013.00935
119. Rehme A.K. and Grefkes C. (2013). Cerebral network disorders after stroke: Evidence from imaging-based connectivity analyses of active and resting brain states in humans. *J. Physiol.* **591**:17–31. DOI:10.1113/jphysiol.2012.243469
120. de Hemptinne C., Swann N.C., Ostrem J.L., et al. (2015). Therapeutic deep brain stimulation reduces cortical phase-amplitude coupling in Parkinson's disease. *Nat Neurosci* **18**:779–786. DOI:10.1038/nn.3997
121. Milekovic T., Sarma A.A., Bacher D., et al. (2018). Stable long-term BCI-enabled communication in ALS and locked-in syndrome using LFP signals. *J Neurophysiol* **120**:343–360. DOI:10.1152/jn.00493.2017
122. Fazli S., Mehnert J., Steinbrink J., et al. (2012). Enhanced performance by a hybrid NIRS-EEG brain computer interface. *Neuroimage* **59**:519–529. DOI:10.1016/j.neuroimage.2011.07.084
123. Craik A., He Y. and Contreras-Vidal J.L. (2019). Deep learning for electroencephalogram (EEG) classification tasks: A review. *J. Neural Eng.* **16**:031001. DOI:10.1088/1741-2552/ab0ab5
124. Biasiucci A., Leeb R., Iturrate I., et al. (2018). Brain-actuated functional electrical stimulation elicits lasting arm motor recovery after stroke. *Nat. Commun.* **9**:2421. DOI:10.1038/s41467-018-04673-z
125. Chen L., Gu B., Wang Z., et al. (2021). EEG-controlled functional electrical stimulation rehabilitation for chronic stroke: System design and clinical application. *Front. Med.* **15**:740–749. DOI:10.1007/s11684-020-0794-5
126. Wagner F.B., Mignardot J.B., Le Goff-Mignardot C.G., et al. (2018). Targeted neurotechnology restores walking in humans with spinal cord injury. *Nature* **563**:65–71. DOI:10.1038/s41586-018-0649-2
127. Lorach H., Galvez A., Spagnolo V., et al. (2023). Walking naturally after spinal cord injury using a brain-spine interface. *Nature* **618**:126–133. DOI:10.1038/s41586-023-06094-5
128. Liu J., Abd-El-Barr M. and Chi J.H. (2016). Long-term training with a brain-machine interface-based gait protocol induces partial neurological recovery in paraplegic patients. *Neurosurgery* **79**:n13–n14. DOI:10.1227/01.neu.0000508601.15824.39
129. Little S., Pogosyan A., Neal S., et al. (2013). Adaptive deep brain stimulation in advanced Parkinson disease. *Ann. Neurol.* **74**:449–457. DOI:10.1002/ana.23951
130. Gilron R., Little S., Perrone R., et al. (2021). Long-term wireless streaming of neural recordings for circuit discovery and adaptive stimulation in individuals with Parkinson's disease. *Nat. Biotechnol.* **39**:1078–1085. DOI:10.1038/s41587-021-00897-5
131. Legon W., Ai L., Bansal P., et al. (2018). Neuromodulation with single-element transcranial focused ultrasound in human thalamus. *Hum. Brain Mapp.* **39**:1995–2006. DOI:10.1002/hbm.23981
132. Pels E.G.M., Aarnoutse E.J., Leinders S., et al. (2019). Stability of a chronic implanted brain-computer interface in late-stage amyotrophic lateral sclerosis. *Clin. Neurophysiol.* **130**:1798–1803. DOI:10.1016/j.clinph.2019.07.020
133. Moly A., Costecalde T., Martel F., et al. (2022). An adaptive closed-loop ECoG decoder for long-term and stable bimanual control of an exoskeleton by a tetraplegic. *J. Neural Eng.* **19**:026021. DOI:10.1088/1741-2552/ac59a0
134. Cummings J., Zhou Y., Lee G., et al. (2023). Alzheimer's disease drug development pipeline: 2023. *Alzheimers Dement.* **9**:e12385. DOI:10.1002/trc2.12385
135. Scheltens P., De Strooper B., Kivipelto M., et al. (2021). Alzheimer's disease. *Lancet* **397**:1577–1590. DOI:10.1016/s0140-6736(20)32205-4
136. Reuben D.B., Kremen S. and Maust D.T. (2024). Dementia prevention and treatment: A narrative review. *JAMA Intern. Med.* **184**:563–572. DOI:10.1001/jamainternmed.2023.8522
137. Jack C.R., Bennett D.A., Blennow K., et al. (2018). NIA-AA research framework: Toward a biological definition of alzheimer's disease. *Alzheimers. Dement.* **14**:535–562. DOI:10.1016/j.jalz.2018.02.018
138. Dubois B., Feldman H.H., Jacova C., et al. (2014). Advancing research diagnostic criteria for Alzheimer's disease: The IWG-2 criteria.*Lancet Neurol.* **13**:614–629. DOI:10.1016/s1474-4422(14)70090-0
139. Jafari Z., Kolb B.E. and Mohajerani M.H. (2020). Neural oscillations and brain stimulation in Alzheimer's disease. *Prog. Neurobiol.* **194**:101878. DOI:10.1016/j.pneurobio.2020.101878
140. Azami H., Zrenner C., Brooks H., et al. (2023). Beta to theta power ratio in EEG periodic components as a potential biomarker in mild cognitive impairment and Alzheimer's dementia. *Alzheimers Res. Ther.* **15**:133. DOI:10.1186/s13195-023-01280-z
141. Özbek Y., Fide E. and Yener G.G. (2021). Resting-state EEG alpha/theta power ratio discriminates early-onset Alzheimer's disease from healthy controls. *Clin. Neurophysiol.* **132**:2019–2031. DOI:10.1016/j.clinph.2021.05.012
142. Kopčanová M., Tait L., Donoghue T., et al. (2024). Resting-state EEG signatures of Alzheimer's disease are driven by periodic but not aperiodic changes. *Neurobiol. Dis.* **190**:106380. DOI:10.1016/j.nbd.2023.106380
143. Jiao B., Li R., Zhou H., et al. (2023). Neural biomarker diagnosis and prediction to mild cognitive impairment and Alzheimer's disease using EEG technology. *Alzheimers Res. Ther.* **15**:32. DOI:10.1186/s13195-023-01181-1
144. Han Y., Wang K., Jia J., et al. (2017). Changes of EEG spectra and functional connectivity during an object-location memory task in Alzheimer's disease. *Front. Behav. Neurosci.* **11**:107. DOI:10.3389/fnbeh.2017.00107
145. Wiesman A.I., Murman D.L., May P.E., et al. (2021). Visuospatial alpha and gamma oscillations scale with the severity of cognitive dysfunction in patients on the Alzheimer's disease spectrum. *Alzheimers Res. Ther.* **13**:139. DOI:10.1186/s13195-021-00881-w
146. Fraga F.J., Mamani G.Q., Johns E., et al. (2018). Early diagnosis of mild cognitive impairment and Alzheimer's with event-related potentials and event-related desynchronization in N-back working memory tasks. *Comput. Meth. Programs Biomed.* **164**:1–13. DOI:10.1016/j.cmpb.2018.06.011

147. Si Y., He R., Jiang L., et al. (2023). Differentiating between Alzheimer's disease and frontotemporal dementia based on the resting-state multilayer EEG network. *IEEE Trans. Neural Syst. Rehabil. Eng.* **31**:4521–4527. DOI:10.1109/tnsre.2023.3329174
148. Lee D.G. and Lee S.B. (2025). Diagnosis of Alzheimer's disease and frontotemporal dementia from electroencephalography signals. *IEEE Trans. Neural Syst. Rehabil. Eng.* **33**:2160–2169. DOI:10.1109/tnsre.2025.3575840
149. Mehraram R., Peraza L.R., Murphy N.R.E., et al. (2022). Functional and structural brain network correlates of visual hallucinations in Lewy body dementia. *Brain* **145**:2190–2205. DOI:10.1093/brain/awac094
150. Brueggen K., Fiala C., Berger C., et al. (2017). Early changes in alpha band power and DMN BOLD activity in Alzheimer's disease: A simultaneous resting state EEG-fMRI study. *Front. Aging Neurosci.* **9**:319. DOI:10.3389/fnagi.2017.00319
151. Chiarelli A.M., Perpetuini D., Croce P., et al. (2021). Evidence of neurovascular uncoupling in mild Alzheimer's disease through multimodal EEG-fNIRS and multivariate analysis of resting-state data. *Biomedicines* **9**:337. DOI:10.3390/biomedicines9040337
152. Colloby S.J., Cromarty R.A., Peraza L.R., et al. (2016). Multimodal EEG-MRI in the differential diagnosis of Alzheimer's disease and dementia with Lewy bodies. *J. Psychiatr. Res.* **78**:48–55. DOI:10.1016/j.jpsychires.2016.03.010
153. Jasodanand V.H., Kowshik S.S., Puducheri S., et al. (2025). AI-driven fusion of multimodal data for Alzheimer's disease biomarker assessment. *Nat. Commun.* **16**:7407. DOI:10.1038/s41467-025-62590-4
154. Anand P. and Singh B. (2013). A review on cholinesterase inhibitors for Alzheimer's disease. *Arch. Pharm. Res.* **36**:375–399. DOI:10.1007/s12272-013-0036-3
155. Dysken M.W., Sano M., Asthana S., et al. (2014). Effect of vitamin E and memantine on functional decline in Alzheimer disease: The TEAM-AD VA cooperative randomized trial. *Jama* **311**:33–44. DOI:10.1001/jama.2013.282834
156. van Dyck C.H., Swanson C.J., Aisen P., et al. (2023). Lecanemab in early Alzheimer's disease. *N. Engl. J. Med.* **388**:9–21. DOI:10.1056/NEJMoa2212948
157. Mintun M.A., Lo A.C., Duggan Evans C., et al. (2021). Donanemab in early Alzheimer's disease. *N. Engl. J. Med.* **384**:1691–1704. DOI:10.1056/NEJMoa2100708
158. Salloway S., Chalkias S., Barkhof F., et al. (2022). Amyloid-related imaging abnormalities in 2 phase 3 studies evaluating aducanumab in patients with early Alzheimer disease. *JAMA Neurol.* **79**:13–21. DOI:10.1001/jamaneurol.2021.4161
159. Kuhn J., Hardenacke K., Lenartz D., et al. (2015). Deep brain stimulation of the nucleus basalis of Meynert in Alzheimer's dementia. *Mol. Psychiatr.* **20**:353–360. DOI:10.1038/mp.2014.32
160. Mao Z.Q., Wang X., Xu X., et al. (2018). Partial improvement in performance of patients with severe Alzheimer's disease at an early stage of fornix deep brain stimulation. *Neural Regen. Res.* **13**:2164–2172. DOI:10.4103/1673-5374.241468
161. Scharre D.W., Weichart E., Nielson D., et al. (2018). Deep brain stimulation of frontal lobe networks to treat Alzheimer's disease. *J. Alzheimers Dis.* **62**:621–633. DOI:10.3233/jad-170082
162. Xu J., Liu B., Shang G., et al. (2025). Efficacy and safety of bilateral deep brain stimulation (DBS) for severe Alzheimer's disease: A comparative analysis of fornix versus basal ganglia of meynert. *CNS Neurosci. Ther.* **31**:e70285. DOI:10.1111/cns.70285
163. Carrarini C., Pappalettera C., Le Pera D., et al. (2024). Non-invasive brain stimulation in cognitive sciences and Alzheimer's disease. *Front. Hum. Neurosci.* **18**:1500502. DOI:10.3389/fnhum.2024.1500502
164. Fathian A., Jamali Y. and Raoufy M.R. (2022). The trend of disruption in the functional brain network topology of Alzheimer's disease. *Sci. Rep.* **12**:14998. DOI:10.1038/s41598-022-18987-y
165. Mencarelli L., Torso M., Borghi I., et al. (2024). Macro and micro structural preservation of grey matter integrity after 24 weeks of rTMS in Alzheimer's disease patients: A pilot study. *Alzheimers Res. Ther.* **16**:152. DOI:10.1186/s13195-024-01501-z
166. Dhaynaut M., Sprugnoli G., Cappon D., et al. (2022). Impact of 40 Hz transcranial alternating current stimulation on cerebral tau burden in patients with Alzheimer's disease: A case series. *J. Alzheimers Dis.* **85**:1667–1676. DOI:10.3233/jad-215072
167. Beisteiner R., Matt E., Fan C., et al. (2020). Transcranial pulse stimulation with ultrasound in Alzheimer's disease-A new navigated focal brain therapy. *Adv. Sci.* **7**:1902583. DOI:10.1002/advs.201902583
168. Teselink J., Bawa K.K., Koo G.K., et al. (2021). Efficacy of non-invasive brain stimulation on global cognition and neuropsychiatric symptoms in Alzheimer's disease and mild cognitive impairment: A meta-analysis and systematic review. *Ageing Res. Rev.* **72**:101499. DOI:10.1016/j.arr.2021.101499
169. Zhang H., Jiao L., Yang S., et al. (2024). Brain-computer interfaces: The innovative key to unlocking neurological conditions. *Int. J. Surg.* **110**:5745–5762. DOI:10.1097/js9.0000000000002022
170. Tazaki M. (2023). A review: Effects of neurofeedback on patients with mild cognitive impairment (MCI), and Alzheimer's disease (AD). *Front. Hum. Neurosci.* **17**:1331436. DOI:10.3389/fnhum.2023.1331436
171. Canny E., Vansteensel M.J., van der Salm S.M.A., et al. (2023). Boosting brain-computer interfaces with functional electrical stimulation: potential applications in people with locked-in syndrome. *J. Neuroeng. Rehabil.* **20**:157. DOI:10.1186/s12984-023-01272-y
172. Liu Z., Tang J., Gao B., et al. (2020). Neural signal analysis with memristor arrays towards high-efficiency brain-machine interfaces. *Nat. Commun.* **11**:4234. DOI:10.1038/s41467-020-18105-4
173. Clark L.A., Cuthbert B., Lewis-Fernández R., et al. (2017). Three approaches to understanding and classifying mental disorder: ICD-11, DSM-5, and the national institute of mental health's research domain criteria (RDoC). *Psychol. Sci. Public Interest* **18**:72–145. DOI:10.1177/1529100617727266
174. Smith K. (2014). Mental health: A world of depression. *Nature* **515**:181. DOI:10.1038/515180a
175. Singh B., Swartz H.A., Cuellar-Barboza A.B., et al. (2025). Bipolar disorder. *Lancet* **406**:963–978. DOI:10.1016/s0140-6736(25)01140-7
176. Borelli C.M. and Solari H. (2019). Schizophrenia. *Jama* **322**:1322. DOI:10.1001/jama.2019.11073
177. Hasin D.S., O'Brien C.P., Auriacombe M., et al. (2013). DSM-5 criteria for substance use disorders: Recommendations and rationale. *Am. J. Psychiatry* **170**:834–851. DOI:10.1176/appi.ajp.2013.12060782
178. Korth C. and Fangerau H. (2020). Blood tests to diagnose schizophrenia: Self-imposed limits in psychiatry. *Lancet Psychiatry* **7**:911–914. DOI:10.1016/s2215-0366(20)30058-4
179. Sarter M. and Tricklebank M. (2012). Revitalizing psychiatric drug discovery. *Nat. Rev. Drug Discov.* **11**:423–424. DOI:10.1038/nrd3755
180. Yang X., McGlynn E., Das R., et al. (2021). Nanotechnology enables novel modalities for neuromodulation. *Adv. Mater.* **33**:e2103208. DOI:10.1002/adma.202103208
181. Öngür D. and Paulus M.P. (2025). Embracing complexity in psychiatry-from reductionistic to systems approaches. *Lancet Psychiatry* **12**:220–227. DOI:10.1016/s2215-0366(24)00334-1
182. Pardiñas A.F., Owen M.J. and Walters J.T.R. (2021). Pharmacogenomics: A road ahead for precision medicine in psychiatry. *Neuron* **109**:3914–3929. DOI:10.1016/j.neuron.2021.09.011
183. Tovino S.A. (2007). Functional neuroimaging and the law: Trends and directions for future scholarship. *Am. J. Bioeth.* **7**:44–56. DOI:10.1080/15265160701518714
184. Zhang Q., Hu S., Talay R., et al. (2023). A prototype closed-loop brain-machine interface for the study and treatment of pain. *Nat. Biomed. Eng.* **7**:533–545. DOI:10.1038/s41551-021-00736-7
185. Roelfsema P.R., Denys D. and Klink P.C. (2018). Mind reading and writing: The future of neurotechnology. *Trends Cogn. Sci.* **22**:598–610. DOI:10.1016/j.tics.2018.04.001
186. Widge A.S., Malone D.A., Jr. and Dougherty D.D. (2018). Closing the loop on deep brain stimulation for treatment-resistant depression. *Front. Neurosci.* **12**:175. DOI:10.3389/fnins.2018.00175
187. Chekroud A.M., Hawrilenko M., Loho H., et al. (2024). Illusory generalizability of clinical prediction models. *Science* **383**:164–167. DOI:10.1126/science.adg8538
188. Duff E.P., Vennart W., Wise R.G., et al. (2015). Learning to identify CNS drug action and efficacy using multistudy fMRI data. *Sci. Transl. Med.* **7**:274ra216. DOI:10.1126/scitranslmed.3008438
189. Feczko E., Miranda-Dominguez O., Marr M., et al. (2019). The heterogeneity problem: Approaches to identify psychiatric subtypes. *Trends Cogn. Sci.* **23**:584–601. DOI:10.1016/j.tics.2019.03.009
190. Hemmings G. (2004). Schizophrenia. *Lancet* **364**:1312–1313. DOI:10.1016/s0140-6736(04)17181-x
191. Jauhar S., Johnstone M. and McKenna P.J. (2022). Schizophrenia. *Lancet* **399**:473–486. DOI:10.1016/s0140-6736(21)01730-x
192. Marder S.R. and Cannon T.D. (2019). Schizophrenia. *N. Engl. J. Med.* **381**:1753–1761. DOI:10.1056/NEJMra1808803
193. Westerink B.H. and Korf J. (1976). Dopamine and schizophrenia. *Lancet* **2**:749. DOI:10.1016/s0140-6736(76)90053-2
194. Chouinard G. and Jones B.D. (1978). Schizophrenia as dopamine-deficiency disease. *Lancet* **2**:99–100. DOI:10.1016/s0140-6736(78)91409-5
195. Belforte J.E., Zsiros V., Sklar E.R., et al. (2010). Postnatal NMDA receptor ablation in corticolimbic interneurons confers schizophrenia-like phenotypes. *Nat. Neurosci.* **13**:76–83. DOI:10.1038/nn.2447
196. Mirnics K., Middleton F.A., Lewis D.A., et al. (2001). Analysis of complex brain disorders with gene expression microarrays: Schizophrenia as a disease of the synapse. *Trends Neurosci.* **24**:479–486. DOI:10.1016/s0166-2236(00)01862-2
197. Zeng L.-L., Wang H., Hu P., et al. (2018). Multi-site diagnostic classification of schizophrenia using discriminant deep learning with functional connectivity MRI. *EBioMedicine* **30**:74–85. DOI:10.1016/j.ebiom.2018.03.017
198. Yan W., Calhoun V., Song M., et al. (2019). Discriminating schizophrenia using recurrent neural network applied on time courses of multi-site FMRI data. *EBioMedicine* **47**:543–552. DOI:10.1016/j.ebiom.2019.08.023
199. Chen H., Lei Y., Li R., et al. (2024). Resting-state EEG dynamic functional connectivity distinguishes non-psychotic major depression, psychotic major depression and schizophrenia. *Mol. Psychiatry* **29**:1088–1098. DOI:10.1038/s41380-023-02395-3
200. Zhu C., Tan Y., Yang S., et al. (2024). Temporal dynamic synchronous functional brain network for schizophrenia classification and lateralization analysis. *IEEE Trans. Med. Imaging* **43**:4307–4318. DOI:10.1109/tmi.2024.3419041
201. Repple J., Gruber M., Mauritz M., et al. (2023). Shared and specific patterns of structural brain connectivity across affective and psychotic disorders. *Biol. Psychiatry* **93**:178–186. DOI:10.1016/j.biopsych.2022.05.031

202. Jiang H., Chen P., Sun Z., et al. (2023). Assisting schizophrenia diagnosis using clinical electroencephalography and interpretable graph neural networks: A real-world and cross-site study. *Neuropsychopharmacology* **48**:1920–1930. DOI:10.1038/s41386-023-01658-5
203. Ahmedt-Aristizabal D., Fernando T., Denman S., et al. (2021). Identification of children at risk of schizophrenia via deep learning and EEG responses. *IEEE J. Biomed. Health Inform.* **25**:69–76. DOI:10.1109/jbhi.2020.2984238
204. Chai C., Ding H., Du X., et al. (2023). Dissociation between neuroanatomical and symptomatic subtypes in schizophrenia. *Eur. Psychiatry* **66**:e78. DOI:10.1192/j.eurpsy.2023.2446
205. Schramm E., Klein D.N., Elsaesser M., et al. (2020). Review of dysthymia and persistent depressive disorder: history, correlates, and clinical implications. *Lancet Psychiatry* **7**:801–812. DOI:10.1016/s2215-0366(20)30099-7
206. Anderson I.M., Haddad P.M. and Scott J. (2012). Bipolar disorder. *Bmj* **345**:e8508. DOI:10.1136/bmj.e8508
207. Gallo S., El-Gazzar A., Zhutovsky P., et al. (2023). Functional connectivity signatures of major depressive disorder: Machine learning analysis of two multicenter neuroimaging studies. *Mol. Psychiatry* **28**:3013–3022. DOI:10.1038/s41380-023-01977-5
208. Kaiser R.H., Whitfield-Gabrieli S., Dillon D.G., et al. (2016). Dynamic resting-state functional connectivity in major depression. *Neuropsychopharmacology* **41**:1822–1830. DOI:10.1038/npp.2015.352
209. Long J.Y., Qin K., Pan N., et al. (2024). Impaired topology and connectivity of grey matter structural networks in major depressive disorder: evidence from a multi-site neuroimaging data-set. *Br. J. Psychiatry* **224**:170–178. DOI:10.1192/bjp.2024.41
210. Yamashita A., Sakai Y., Yamada T., et al. (2020). Generalizable brain network markers of major depressive disorder across multiple imaging sites. *PLoS Biol* **18**:e3000966. DOI:10.1371/journal.pbio.3000966
211. Wen J., Antoniades M., Yang Z., et al. (2024). Dimensional neuroimaging endophenotypes: Neurobiological representations of disease heterogeneity through machine learning. *Biol. Psychiatry* **96**:564–584. DOI:10.1016/j.biopsych.2024.04.017
212. Nunes A., Schnack H.G., Ching C.R.K., et al. (2020). Using structural MRI to identify bipolar disorders - 13 site machine learning study in 3020 individuals from the ENIGMA Bipolar Disorders Working Group. *Mol. Psychiatry* **25**:2130–2143. DOI:10.1038/s41380-018-0228-9
213. Calesella F., Serra E., Palladini M., et al. (2025). Differences in resting-state functional connectivity between depressed bipolar and major depressive disorder patients: A machine learning study. *Eur. Neuropsychopharmacol.* **97**:28–37. DOI:10.1016/j.euroneuro.2025.05.011
214. Pan N., Qin K., Patino L.R., et al. (2024). Aberrant brain network topology in youth with a familial risk for bipolar disorder: A task-based fMRI connectome study. *J. Child Psychol. Psychiatry* **65**:1072–1086. DOI:10.1111/jcpp.13946
215. Vai B., Parenti L., Bollettini I., et al. (2020). Predicting differential diagnosis between bipolar and unipolar depression with multiple kernel learning on multimodal structural neuroimaging. *Eur. Neuropsychopharmacol.* **34**:28–38. DOI:10.1016/j.euroneuro.2020.03.008
216. Sankar A., Shen X., Colic L., et al. (2023). Predicting depressed and elevated mood symptomatology in bipolar disorder using brain functional connectomes. *Psychol. Med.* **53**:6656–6665. DOI:10.1017/s003329172300003x
217. Imperio C.G., Levin F.R. and Martinez D. (2024). The neurocircuitry of substance use disorder, treatment, and change: A resource for clinical psychiatrists. *Am. J. Psychiatry* **181**:958–972. DOI:10.1176/appi.ajp.20231023
218. Koban L., Wager T.D. and Kober H. (2023). A neuromarker for drug and food craving distinguishes drug users from non-users. *Nat. Neurosci.* **26**:316–325. DOI:10.1038/s41593-022-01228-w
219. Owens B. (2015). Addiction. *Nature* **522**:S45. DOI:10.1038/522S45a
220. Robinson T.E. and Berridge K. C. (2025). The incentive-sensitization theory of addiction 30 years on. *Annu. Rev. Psychol.* **76**:29–58. DOI:10.1146/annurev-psych-011624-024031
221. Goutaudier R., Joly F., Mallet D., et al. (2023). Hypodopaminergic state of the nigrostriatal pathway drives compulsive alcohol use. *Mol. Psychiatry* **28**:463–474. DOI:10.1038/s41380-022-01848-5
222. Kasanetz F., Lafourcade M., Deroche-Gamonet V., et al. (2013). Prefrontal synaptic markers of cocaine addiction-like behavior in rats. *Mol. Psychiatry* **18**:729–737. DOI:10.1038/mp.2012.59
223. Huang S., Liu X., Li Z., et al. (2025). Memory reconsolidation updating in substance addiction: Applications, mechanisms, and future prospects for clinical therapeutics. *Neurosci. Bull.* **41**:289–304. DOI:10.1007/s12264-024-01294-z
224. Garrison K.A., Sinha R., Potenza M.N., et al. (2023). Transdiagnostic connectome-based prediction of craving. *Am. J. Psychiatry* **180**:445–453. DOI:10.1176/appi.ajp.21121207
225. Parvaz M.A., Moeller S.J. and Goldstein R.Z. (2016). Incubation of cue-induced craving in adults addicted to cocaine measured by electroencephalography. *JAMA Psychiatry* **73**:1127–1134. DOI:10.1001/jamapsychiatry.2016.2181
226. Lichenstein S.D., Kohler R., Ye F., et al. (2023). Distinct neural networks predict cocaine versus cannabis treatment outcomes. *Mol. Psychiatry* **28**:3365–3372. DOI:10.1038/s41380-023-02120-0
227. Wang Y., Li D., Widjaja J., et al. (2024). An electroencephalogram signature of melanin-concentrating hormone neuron activities predicts cocaine seeking. *Biol. Psychiatry* **96**:739–751. DOI:10.1016/j.biopsych.2024.04.009
228. Morris L.S., Kundu P., Baek K., et al. (2016). Jumping the gun: Mapping neural correlates of waiting impulsivity and relevance across alcohol misuse. *Biol. Psychiatry* **79**:499–507. DOI:10.1016/j.biopsych.2015.06.009
229. Kobayashi M. and Pascual-Leone A. (2003). Transcranial magnetic stimulation in neurology. *Lancet Neurol.* **2**:145–156. DOI:10.1016/s1474-4422(03)00321-1
230. Ferrarelli F. and Phillips M.L. (2021). Examining and modulating neural circuits in psychiatric disorders with transcranial magnetic stimulation and electroencephalography: Present practices and future developments. *Am. J. Psychiatry* **178**:400–413. DOI:10.1176/appi.ajp.2020.20071050
231. Cho H., Razza L.B., Borrione L., et al. (2022). Transcranial electrical stimulation for psychiatric disorders in adults: A Primer. *Focus* **20**:19–31. DOI:10.1176/appi.focus.20210020
232. Rabany L., Deutsch L. and Levkovitz Y. (2014). Double-blind, randomized sham controlled study of deep-TMS add-on treatment for negative symptoms and cognitive deficits in schizophrenia. *J. Psychopharmacol.* **28**:686–690. DOI:10.1177/0269881114533600
233. Neufeld N.H. and Blumberger D.M. (2025). An update on the use of neuromodulation strategies in the treatment of schizophrenia. *Am. J. Psychiatry* **182**:332–340. DOI:10.1176/appi.ajp.20250068
234. Dlabac-de Lange J.J., Knegtering R. and Aleman A. (2010). Repetitive transcranial magnetic stimulation for negative symptoms of schizophrenia: Review and meta-analysis. *J Clin Psychiatry* **71**:411–418. DOI:10.4088/JCP.08r04808yel
235. Diana M., Raij T., Melis M., et al. (2017). Rehabilitating the addicted brain with transcranial magnetic stimulation. *Nat. Rev. Neurosci.* **18**:685–693. DOI:10.1038/nrn.2017.113
236. Bormann N.L., Oesterle T.S., Arndt S., et al. (2024). Systematic review and meta-analysis: Combining transcranial magnetic stimulation or direct current stimulation with pharmacotherapy for treatment of substance use disorders. *Am J Addict* **33**:269–282. DOI:10.1111/ajad.13517
237. Herrold A.A., Kletzel S.L., Harton B.C., et al. (2014). Transcranial magnetic stimulation: Potential treatment for co-occurring alcohol, traumatic brain injury and posttraumatic stress disorders. *Neural Regen. Res.* **9**:1712–1730. DOI:10.4103/1673-5374.143408
238. Angeles-Valdez D., Rasgado-Toledo J., Villicaña V., et al. (2024). The Mexican dataset of a repetitive transcranial magnetic stimulation clinical trial on cocaine use disorder patients: SUDMEX TMS. *Sci. Data* **11**:408. DOI:10.1038/s41597-024-03242-y
239. West E.A., Niedringhaus M., Ortega H.K., et al. (2021). Noninvasive brain stimulation rescues cocaine-induced prefrontal hypoactivity and restores flexible behavior. *Biol Psychiatry* **89**:1001–1011. DOI:10.1016/j.biopsych.2020.12.027
240. Camchong J., Roediger D., Fiecas M., et al. (2023). Frontal tDCS reduces alcohol relapse rates by increasing connections from left dorsolateral prefrontal cortex to addiction networks. *Brain Stimul.* **16**:1032–1040. DOI:10.1016/j.brs.2023.06.011
241. Zhang H., Rajji T.K., Selby P., et al. (2023). Augmenting varenicline treatment with transcranial direct current stimulation (tDCS) increases smoking abstinence rates at end of treatment. *Brain Stimul.* **16**:1083–1085. DOI:10.1016/j.brs.2023.07.001
242. Zangen A., Moshe H., Martinez D., et al. (2021). Repetitive transcranial magnetic stimulation for smoking cessation: A pivotal multicenter double-blind randomized controlled trial. *World Psychiatry* **20**:397–404. DOI:10.1002/wps.20905
243. Ibrahim C., Tang V.M., Blumberger D.M., et al. (2024). Repetitive transcranial magnetic stimulation for smoking cessation. *Cmaj* **196**:E187–e190. DOI:10.1503/cmaj.230806
244. Horn A., Li N., Meyer G.M., et al. (2025). Deep brain stimulation response circuits in obsessive-compulsive disorder. *Biol Psychiatry.* DOI:10.1016/j.biopsych.2025.03.008
245. Coenen V.A., Bewernick B.H., Kayser S., et al. (2019). Superolateral medial forebrain bundle deep brain stimulation in major depression: A gateway trial. *Neuropsychopharmacology* **44**:1224–1232. DOI:10.1038/s41386-019-0369-9
246. Provenza N.R., Sheth S.A., Dastin-van Rijn E.M., et al. (2021). Long-term ecological assessment of intracranial electrophysiology synchronized to behavioral markers in obsessive-compulsive disorder. *Nat. Med.* **27**:2154–2164. DOI:10.1038/s41591-021-01550-z
247. Faller J., Doose J., Sun X., et al. (2022). Daily prefrontal closed-loop repetitive transcranial magnetic stimulation (rTMS) produces progressive EEG quasi-alpha phase entrainment in depressed adults. *Brain Stimul* **15**:458–471. DOI:10.1016/j.brs.2022.02.008
248. Wischnewski M., Shirinpour S., Alekseichuk I., et al. (2024). Real-time TMS-EEG for brain state-controlled research and precision treatment: A narrative review and guide. *J Neural Eng* **21**:061001. DOI:10.1088/1741-2552/ad8a8e
249. Chen H., Liu T., Song Y., et al. (2025). State-Dependent transcranial magnetic stimulation synchronized with electroencephalography: Mechanisms, applications, and future directions. *Brain Sci.* **15**:731. DOI:10.3390/brainsci15070731
250. Grossman N., Bono D., Dedic N., et al. (2017). Noninvasive deep brain stimulation via temporally interfering electric fields. *Cell* **169**:1029–1041. DOI:10.1016/j.cell.2017.05.024
251. Wang S., Chen J., Wang L., et al. (2025). Individualized transcranial temporal interference stimulation (tTIS) for cognitive impairments and negative symptoms in

patients with schizophrenia: A study protocol for a randomized controlled trial. *BMC Psychiatry* **25**:714. DOI:10.1186/s12888-025-07158-8
252. Demchenko I., Rampersad S., Datta A., et al. (2024). Target engagement of the subgenual anterior cingulate cortex with transcranial temporal interference stimulation in major depressive disorder: A protocol for a randomized sham-controlled trial. *Front. Neurosci.* **18**:1390250. DOI:10.3389/fnins.2024.1390250
253. Zhou H., Wang M., Qi S., et al. (2025). Transcranial temporal interference stimulation for treating bipolar disorder with depressive episodes: A feasibility study. *Mol. Psychiatr.* **2025**:1–8. DOI:10.1038/s41380-025-03292-7

FUNDING AND ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (T2322020, 62371329, T2322021, 82271218, 82471514), National Key R&D Program of China (2024YFF1206500, 2022YFF1202500, 2023YFF1203500), STI2030-Major Projects (2022ZD0214500). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

AUTHOR CONTRIBUTIONS

All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

Biao Sun is an Editorial Board member of The Innovation journals and was blinded from reviewing or making final decisions on the manuscript. Peer review was handled independently of this member and their research group. The other authors declare no conflicts of interest.

ETHICAL STATEMENT AND PATIENT CONSENT

Not Applicable.

LEAD CONTACT WEBSITE

Intelligent Electronics Laboratory, Tianjin University. Website: https://sunlab.top/